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Radioactivity and Health A History

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Radioactivity and Health: A History

*To disseminate knowledge is to
disseminate prosperity—I mean
general prosperity not individual
riches—and with prosperity
disappears the greater part of
the evil which is our heritage
from darker times.*

Alfred Nobel

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FOREWORD

The invention of the cyclotron, the construction of nuclear reactors, and the explosion of nuclear weapons unleashed upon the world vast quantities of new substances, radioactive isotopes, that created unprecedented opportunities and problems for mankind, far beyond those posed by the radioactive isotopes that occur naturally in the earth. The availability of cyclotron-produced radioisotopes in the 1930s was quickly seized upon by medical scientists who saw opportunities for their use in diagnosis and therapy and by biological and chemical scientists to put radioactive labels on chemical compounds to trace them through chemical and biological processes. However, except for the saga of the radium dial painters and patients, the serious efforts began in the 1940s with the discovery of fission and the construction of nuclear reactors, which led to large quantities of many radioisotopes becoming available. This also stimulated concern about the potential health risks associated with the production and use of radioactive isotopes and led to the development of a large health and environmental research program by the Manhattan Engineer District (MED) and Atomic Energy Commission (AEC), which also undertook research on the medical applications of radioisotopes.

Thus began an important and productive period in biological and medical research in the United States, which led the world in understanding the behavior of radioactive isotopes in living organisms and the environment. How these research programs developed, who developed them, and the progression of scientific knowledge about radioisotopes in biological material and the environment should not be lost from the record of major accomplishments of the MED, the AEC, and its successor agencies, the Energy Research and Development Administration, and the Department of Energy. Dr. J. Newell Stannard's *Radioactivity and Health: A History* assures that will not happen. It is a fascinating story of scientific research and of people who provided leadership and made important discoveries. It is the story of how science successfully dealt with the potential hazards of working with highly radioactive material; undertook research to understand its behavior and effects in biological and environmental media; applied this knowledge to the technology for handling radioisotopes safely and to the establishment of radiation protection standards, which have guided the design of laboratories, hospitals, and factories where radioisotopes are produced and used.

Newell Stannard, being part of this important scientific endeavor and acquainted with all of the principal scientists and administrators involved, has accomplished a monumental task in writing this volume, capturing in it the essence of these scientific achievements. This volume is much more than a history of a particular segment of science, documenting who did what and when;

it also deals with the development of scientific concepts, the progression of discoveries, the events that paralleled and influenced the scientific program, and the application of the knowledge to protection of human beings and the environment. Newell is eminently qualified to have written this history because he was a pioneer in research on health effects of radioisotopes, and he has continued to contribute to the field in numerous ways for fifty years. A brief summary of his career will help the reader recognize his qualifications and understand his incentive for writing this history.

During World War II, Newell spent several years doing research on respiratory physiology, as a naval officer at the Bureau of Medicine and Surgery in Washington, D.C., and also as a member of the staff at the National Institute of Health. After the war, he was invited to the University of Rochester School of Medicine to establish a graduate education program in the field of atomic energy as applied to health sciences. Beginning as assistant professor of radiation biology and chief of the radiation toxicology section in the Atomic Energy Project, he became its assistant director for education in 1948, when the first AEC fellowship students arrived at the University to begin a year of graduate study in radiological physics (later to be called health physics). Under Newell's leadership, this master's degree program was soon expanded to include Ph.D. programs in radiation biology, biophysics, and toxicology. These were the world's first Ph.D. programs that applied atomic energy to the life sciences and medicine. The AEC Fellows were soon joined by graduate students from all of the U.S. armed forces, including medical officers, for advanced courses in nuclear science, and by students from throughout the world sponsored by the International Atomic Energy Agency.

Newell began his own radiobiological research in two areas: effects of radiation on cell membranes and the biological effects of alpha-emitting radionuclides. The first represented an early attempt to understand the mechanism of the interaction of ionizing radiation on living cells. The second was directed primarily at developing information about the behavior and biological effects of polonium. Polonium, an alpha-particle emitter, was an early component of nuclear weapons and was being handled in relatively large quantities at MED and AEC laboratories and production plants. The research accomplished by Newell and his colleagues is the definitive work on the biological aspects of polonium and was a significant biomedical contribution to the atomic weapons program.

Newell and a colleague carried out one of the first repeated-insult studies by administering regular/periodic doses of polonium to rats by intravenous injection, to study the pathological findings of radiation under a relatively constant body burden. By comparing the findings in rats with a maintained body burden to those observed following a single injection, they were able to make comparisons that had widespread practical implications.

Newell's work with polonium and his earlier work in respiratory physiology led to his being given responsibility at the University of Rochester, in about 1952, for research on the inhalation of radioactive aerosols. Although the Atomic Energy Project at the University already had more than five years' experience exposing animals to aerosols of uranium compounds, this new program was the first to involve highly radioactive alpha-emitting materials such as polonium and plutonium. Newell is therefore truly the founding father of research on inhaled radionuclides. He and his associates developed completely new methodologies for containing radioactive aerosols for exposing rodents and dogs by inhalation,

while avoiding contamination of personnel and of facilities in which the work was performed. This was the beginning of a program that trained many graduate students who contributed not only to research on inhaled radionuclides at Rochester but carried the techniques to programs at other laboratories. Newell's pioneering work at the University of Rochester became a basis for the AEC's large programs on inhaled radionuclides at other institutions.

Newell was a program director in Test Group 57 of Operation Plumbbob and, as such, had responsibility for organizing and carrying out various biological experiments at the Nevada Test Site. These field studies were aimed at assessing the risks associated with nonnuclear accidents involving nuclear weapons. Results from this work serve as a basis for certain present safety criteria in the weapons program, and they represent a one-time collection of crucial data from a type of study that will never again be repeated. He was able to add some quality assurance philosophy to studies carried out under field conditions and, thus, added greatly to the credibility of biologically oriented field trials.

In addition to this work in radiation toxicology, Newell recognized early the importance of understanding the physical-chemical behavior of solutions and suspensions of radionuclides. Only with the atomic age was one able to measure the chemistry of extremely low concentrations under a wide range of pH. Under Newell's supervision, knowledge of the behavior of radiocolloidal suspensions greatly expanded. The relationship of radiocolloidal suspensions formed under various chemical conditions to their metabolic behavior in experimental animals added significantly to our quantitation of the role of the reticuloendothelial system as a function of the physical-chemical state of a substance entering the circulatory system. Such work emphasized Newell's versatility in scientific fields that at times diverged greatly from his basic education and training.

Newell's educational and research activities have been vital to many programs related to atomic energy, including nuclear medicine, nuclear power, weapons, and space. Hundreds of graduates from the programs developed under his supervision can today be found in positions of responsibility in research and in radiation protection—in government agencies such as the Department of Energy, Nuclear Regulatory Commission, Environmental Protection Agency, National Institutes of Health; in the armed forces; in nearly all U.S. nuclear power plants; in national laboratories; in universities; and in hospitals.

Throughout his career, Newell has served with distinction on numerous national and international committees concerned with radiation protection. His publications, numbering well over one hundred, represent significant contributions to the study of radioactivity and health.

Newell is a rarity among men and among scientists. His dedication to the monumental task this book represents attests to that, especially because he undertook the project after retiring from his dynamic and productive teaching and research career. Newell's professional achievements are matched by his extraordinary personal virtues. He is thoughtful, compassionate, trusting, and friendly; he always sees the best in everyone.

It is frequently lamented that major scientific endeavors are not documented while the principals are living. This book addresses that problem directly. In preparing it, Newell interviewed nearly all those who made the scientific contributions discussed and those who made the decisions that implemented the research. In some instances, when people were interviewed long after the events, Newell noted the differences in their individual memories. He has skillfully dealt with these discrepancies so that history is served without personal bias.

In addition to the personal interviews, Newell conducted a massive literature search, visiting libraries throughout the country. His references include citations of obscure publications and previously classified material, as well as the vast open literature produced over the past century. His task has been long and arduous, but one he has undertaken with enthusiasm and consummate skill. He has not been alone in his endeavor. Dr. Raymond Baalman, of Battelle, worked closely with Newell throughout. Ray, like Newell, is a rarity for a scientific research institution. After earning a doctorate in French literature and teaching several years, Ray was invited to join the Environment, Health and Safety Research Program at Pacific Northwest Laboratory as scientific editor and writer. He demonstrated exceptional skills in working with scientists to prepare technical papers and reports. One of his early major assignments was to assist the author of this Foreword in the preparation of a report for the International Commission on Radiological Protection, which appeared as ICRP Publication 31, *The Biological Effects of Inhaled Radionuclides*. With this background, he was well prepared to work with Newell throughout the production of this comprehensive history of the research conducted on the health and environmental aspects of radionuclides.

This book is a valuable contribution to the history of science because it records in a cogent and clear manner this extraordinary period of scientific accomplishments. It will help government administrators understand the past as they plan future research programs; will tell young scientists entering the field what has come before and who has made significant contributions; will remind those scientists who participated in the research of the magnitude of this important segment of American science; and will help those responsible for establishing and recommending radiation protection standards know what information is available. Finally, it will reassure those working with radionuclides and members of the public that the protection of their health and that of their descendants, as well as the protection of the environment in which they live, has been addressed in a major scientific endeavor for more than a half century.

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PREFACE

I. Purpose and Scope

This book concerns a facet of biomedical science that has had less systematic review than many other aspects, with a few notable exceptions. It concerns the history of our understanding of the behavior of radioactive materials (radioisotopes, radionuclides) in living organisms and in the environment and the gradual acquisition of knowledge regarding their effects. There can be no doubt that many thousands of lives have been saved, prolonged, or made more tolerable by the myriad uses of radioactive materials in clinical medicine. This began with the use of radium as a source of gamma rays and continues through today in the use of very large radioisotope sources and in the very active field of nuclear medicine. In addition, many thousands more of us have been affected positively by the biomedical discoveries made possible by the uses of radioisotopes as tracers in the study of biological processes. In the aggregate, these beneficial effects outweigh, by far, even the horrendous casualties of the atomic bombings of Japan. However, they do not attract as much attention, because they occur one by one.

Research on the biological effects of ionizing radiation began long before atomic bombs, weapons testing, fallout, or other modern concerns. It began quite soon after the discovery of x rays by Roentgen. Historical accounts have been many and ample, but, in general, they emphasize the biological effects of ionizing radiation from sources external to the body, such as x rays, gamma rays, neutrons, etc. Comprehensive historical reviews of the work with radioactive materials have not been so numerous or so ample, even though the history begins as early as the fifteenth century. Work with radioisotopes has always been inherently more complex than that with external sources, because the radionuclides behave chemically like their nonradioactive congeners and have, in addition, the complexities of differences in chemical form. Thus, their dosimetry is difficult indeed. As a result, investigators interested in basic mechanisms quite naturally chose sources with fewer complexities and sources that could be turned off at the flick of a switch rather than lingering (and delivering dose) for varying lengths of time. Nevertheless, the accumulated information with radionuclides is now substantial, even unwieldy in volume, and a formal history is clearly in order.

There are other reasons for this effort. The book concerns facets of a period of American scientific and technological history that can never be repeated, viz., the release of the energy of the atom. There are those who bemoan man's discovery of the energy in the atomic nucleus and ways to release it and state that the world would be much better off had the discovery not been made.

Such reasoning is specious. Renowned physicists have stated many times that once radioactivity had been discovered it was only a matter of time before the obviously high energies were made subject to release. When Lise Meitner described uranium fission and its energy release just before the storm of World War II broke, it became clear that the only cogent question was who would get there first. Would those who bemoan our efforts toward the release of atomic energy feel the world would now be a better place if Hitler had gotten there first? We had no choice.

In this context, a distinguished cadre of biologists and physicians devoted all of their energies for many years, during and after World War II, to protecting the workers, communities, and the environment generally from the possible deleterious effects of the enormous quantities of radioactivity expected to be produced, if the process worked; also, to learning as much as possible about the behavior of the numerous old and new substances in the body and their effects. Fortunately, they could build upon the experience already gained with radium, e.g., the dial painters, radium chemists, and patients who received radium as a therapeutic nostrum; early experiences with other naturally occurring radionuclides; and the growing amount of information concerning the uranium miners, particularly in Europe. This book describes these early beginnings, as well as the World-War-II and post-World-War-II investigations that were its initial *raison d'être*.^(a)

It should be clear that the hundreds of biomedical scientists involved in those efforts mounted complex long-term experiments whose results were slow to come, maddeningly slow, compared to parallel efforts in fields like molecular biology. Some of the work is still in progress, and more needs to be done. Nevertheless, at every turn, these investigators' eyes were peeled for any indications of revelation of a new phenomenon of nature or modifications of older phenomena. Contributions to "basic" mechanistic research were significant though less obvious than a similar effort in a field less oriented to practical matters.^(b)

Even though there is much yet to learn, the intensity of work in this field (except for that in nuclear medicine) is much lower now than in the days of peak activity. There are many reasons. The largest mysteries have been uncovered, even solved to some degree. The problems of chemical toxicology are now requiring efforts not dissimilar to those in the most active days of radionuclide research. Competition for funds is fierce, thanks to the federal deficit and a general disinclination to spend at the old rate on nuclear matters, no matter how far they may be from bombs or reactors. A few of the researchers most involved have become discouraged and disillusioned. As they approach the closing days of their careers, they wonder if their efforts made any difference or were appreciated. It is hoped that the substance of this book can help such individuals to renewed enthusiasm for their contributions and those of their colleagues. Those coming upon the story for the first time or for a first

(a) The initial idea for the book was to unearth and describe facets of the World War II effort that had never been published. However, the author's New England conscience would not allow so circumscribed an effort. Instead, he decided to go back to the earliest experiences and follow through on all possible fronts, except actual clinical medicine. The result is a more unwieldy but, he hopes, a more useful volume.

(b) It is hoped that many of the leads coming from these works can now be followed out in more frankly mechanistic experiments (see chapter 21).

broad look should develop a sense of pride in the accomplishments and gratitude to the people who contributed so generously of life and substance for relatively modest material rewards.

II. The Modus Operandi

This book is designed to be primarily a history of research facts, measurements, and ideas and the people who developed them. "Research" is defined very broadly to include from bench-top laboratory experiments to worldwide environmental investigations. The book is not a monograph or a critical review. The findings and conclusions are presented largely as the investigators saw and reported them. Frequently, the discussion utilizes the terminology and units of the time, unless they are truly antiquated or potentially unclear. It is only when the work being reported is markedly iconoclastic or obviously wrong that I chose to make special note of it or to correct it. Nevertheless, except for direct quotations, the language is mine, and I take full responsibility for it.

The working materials for this volume included published papers in scientific journals, books, published conferences and symposia, personal interviews with over 100 individuals, some of them more than once (see Appendix A), and, particularly for the 1940-1950 decade and for the large government-supported laboratories to the present day, "in-house" reports. These reports frequently represent the only comprehensive archive of what was done and why. Unfortunately, this source is drying up because of storage problems and must be retrieved by ever more complex and inconvenient means. For this reason, special efforts have been taken to review and document these sources, though even now some sections of the field are partially inaccessible.^(a) Nevertheless, the volume of all materials available for this review was surprisingly large and the quality much better than might have been expected for so complex and disparate a field approached under conditions of considerable urgency. It did require diligent searching, however!

For convenience, the book is divided into the following major sections:

- I. Naturally Occurring Radioactive Elements (chapters 1-4)
- II. The Manmade Radioisotopes (chapters 5-8)
- III. Inhalation Toxicology (chapters 9 and 10)
- IV. Environment Chapters (chapters 11-15)
- V. Instrumentation (chapters 17 and 18)
 - chapter 17 written by Howard L. Andrews
 - chapter 18 written by Ronald L. Kathren
- VI. Therapy and Nuclear Medicine (chapters 19 and 20)
- VII. Concluding Comments (chapter 21)

The reader is invited to explore further the planned contents of each major section by perusal of its individual preface and the several chapter headings and outlines.

The basic pattern is chronological, but in moderately large chunks. Slavish devotion to a year-by-year rendition of the events was considered both

(a) Poor housekeeping and/or lack of foresight have made their contributions to this inaccessibility. Only in rare instances did a continued high-security classification exclude a document from citation in this chronicle.

unnecessary and likely to be boring. The time quanta are, instead, chosen to fit the progression of events in the subject under discussion. However, to aid the reader interested in specific years and a moderately fine-tuned chronology, all chapters, except the summary one (chapter 21), contain a "Capsule Chronology," which selects out pertinent events by year.

Historical treatises in science can be relieved somewhat of the ever-present urge to be current or present the latest information. In the initial stages, it was decided to cut off detailed accounts at about 1980. As the project grew, it became necessary to discuss events of more recent years, especially if important new developments occurred that bore on the subject at hand. Many of these are handled by "Notes Added in Proof." A short discussion of the bearing of the researches described herein on the Chernobyl reactor incident has been added to the final chapter. Nevertheless, the reader should not assume that routine developments since about 1980 will be included. The recent literature is readily available for these.

Since our focus is largely on programs and the people and places involved, many of the chapters present developments institution by institution. In other cases, e.g., the uranium-miner saga, the contributions of single institutions merged to such an extent that the progression of ideas and findings seemed more pertinent than the individual institutions. Even so, the contributions of people and places are kept distinct. There is little anonymity anywhere in the book.

For the reader's convenience, each chapter (with a few exceptions) has also an Overview, which tells what it is proposed to cover; an Outline; and a Summary and Commentary, which allow some generalizations on what was said in the chapter. Each of these was considered important for so long a work. Nevertheless, they make no pretense at complete coverage. These, along with the "Capsule Chronologies," should provide a useful synopsis of the material in the text.^(a)

It has been necessary to concentrate on work done in the United States, especially for certain periods. This is especially true for the years of World War II. In much of the research, there was no one else working on it at this time! For the pre-World-War-II years, by contrast, the discussion could be much more international. Indeed it could be nothing else. For the post-World-War-II years, the sheer volume of new research made selection necessary. The author's research experience and the sponsorship (but not control) of the work indirectly by the U.S. Department of Energy (see Acknowledgments) also led to emphasis on work in or concerning U.S. laboratories. In some areas, much worthy work done in other countries had to be given short shrift, and this is regretted.^(b) In other areas (e.g., chapter 19 on therapeutic removal of deposited radionuclides), U.S. contributions and those of other countries were so inextricably bound together that the chapter is a presentation of efforts throughout the world.

Obviously, precision and sensitivity of measurements changed markedly over the years of this review. There is now greater precision and less variability. The chapters on instrumentation reflect briefly on this fact. However, since the

(a) The author's worries about the considerable length of this history were assuaged by the sponsor's encouragement to do a "complete job," for it would "never be done again."

(b) Perhaps there will be an opportunity to make up this deficiency in another work.

1920s, except for de novo developments such as accelerators, nuclear reactors, whole-body counters, etc., the improvements have done more to change convenience and reliability than the fundamental ideas about biological phenomena that could be deduced from the measurements. We take several occasions to salute the skill of the early investigators for finding as much as they did with primitive and temperamental methodology. Instances where improved methodology brought a quantum jump in ideas are singled out. Otherwise, the gradual improvement in measurement abilities and in sophistication of ideas is considered an inherent part of the developments chronicled, and readers are expected to take their cue from the date of the work under discussion.

In any work of this length done primarily by a single author, and despite the diligent efforts of an excellent editor and many reviewers, some errors are bound to have slipped by. They may have been sins of omission as well as commission. For these, the author takes full responsibility. Also, much worthy research had to be consciously omitted. The author takes full responsibility for such omissions, also. (Something had to be done to save space!) If there are serious errors or omissions, the author would appreciate knowing and will do what he can to make adjustments.

A word about the ordering of the reference lists might be helpful. References are grouped at the end of each chapter in the following way: multiple citations of a single author, in chronological order; two or three authors, in alphabetical order and then chronologically, if necessary; four or more authors are treated as "et al." in the text and are grouped alphabetically and then chronologically in the reference list. Tables and figures taken from other works have been reset and redrawn, preserving, in most instances, the original captions, units, footnote styles, and so forth. Modifications have been noted. My notes to tables are set below the full rule at the end of the table.

Finally, let it be mentioned in closing this section:

The losses of history are indeed irretrievable; when productions of fancy or science have been swept away, new poets may invent and new philosophers may reason; but if the inscription of a single fact be obliterated, it can never be restored by the united effort of genius or industry. (Edward Gibbon, *Miscellaneous Works*, III. 561.)

Surely not all "facts" are so immortal, nor can we ever hope to keep them all. Science is a continuum. Nevertheless, the present volume tries to preserve as much as reasonably achievable from a special facet of a special era. Readers are privileged to skip facts when they become too numerous, but it is hoped they will follow the trains of thought.

III. Acknowledgments

One of the grand emoluments of teaching is to see the extension and maturation in students of what the teacher could play a part in initiating. The author has been privileged to have a part in launching the careers of many excellent scientists who have gone on to productive and important places in our particular sphere. For this book, the author is profoundly grateful to his first Ph.D. student at the University of Rochester, Dr. William J. Bair, now Manager of the Life Sciences Center at Battelle, Pacific Northwest Laboratories. Dr. Bair, along with Dr. Bruce Wachholz, another Rochester graduate, first suggested the idea. Dr. Bair stimulated and managed a contract between the Department of Energy and Battelle on which the author became a consultant. He graciously accepted, indeed encouraged, a considerable expansion of the scope of the project and

has been patient as the time extended well beyond what was originally anticipated. Furthermore, he has read every chapter and contributed important suggestions from his broad experience. Finally, Dr. Bair provided needed technical assistance from his organization in the preparation of figures, word processing, typesetting, and many other operations not available to someone, like myself, in retired status.

Second, the author wishes to express his gratitude to Dr. Ray W. Baalman, senior editor/writer in the Life Sciences Center at Battelle, Pacific Northwest Laboratories, and admiration for his skillful and productive editorial work. Indeed, this book has, at certain periods, I am sure, consumed almost all of Dr. Baalman's time and become almost as much a part of his life as it has of mine. It takes special talent to be an editor who can impose high standards, yet avoid nitpicking or unduly pressing his own ideas of writing style. I hope Dr. Baalman has learned as much about science from this effort as I have learned about language from him. Dr. Baalman used *A Manual of Style* from the Chicago Press as his guide.

The book was typeset at Battelle, preliminarily by Mrs. Mary Jochen and Mrs. Sue Vickerman. This monumental task was taken over by Mrs. Sandie Blakley, a typesetter par excellence, who could spot a column of figures that did not add up correctly, as well as inconsistencies in mathematical notation. She also did the lay-up of the final manuscript, with assistance from Mrs. Sara Nelson and Mrs. Rose Watt, who, in addition, typeset the indexes from copy typed by Mrs. Marianna Cross. The cover was designed by Ms. Dorothy Siebe of Boeing Computer Services, Richland.

Dr. Baalman received editorial assistance on the references from Ms. Kelly Parnell and Ms. Terri Gilbride, and on the indexes from Ms. Dev Felton, all of Battelle. Mrs. Jan Tarantino helped to ensure the quality of the book's appearance, assisting the editorial staff with her keen eye for detail.

The author is not an instrument man, even though he appreciates the importance of using the best available, kept in the best of condition. He was very fortunate to persuade Dr. Howard Andrews, PHS retired and emeritus from the University of Rochester, now living in Jamestown, Rhode Island, to prepare a chapter on the major developments in laboratory instrumentation for detection and measurement of radioactivity and Ronald Kathren, of Battelle and the Hanford Environmental Health Foundation for a chapter on the history and development of instrumentation for field use and for monitoring. Both have had long experience in the area. In addition, Kathren is an aficionado in the history of the science of radiation and has a collection of old instruments.

In Appendix A, the numerous interviews carried out by the author are listed by name, place, and date. Thanks go to all who gave generously of their time and talents for a quasi-oral history used to start the project. Many of these individuals and others read chapters or portions of chapters for accuracy and coincidence with their personal experiences. Among these are Edward Alpen, Howard Andrews, William J. Bair, Robert Bennett, Leo Bustad, Austin Brues, Melvin Carter, Arland Carsten, George Casarett, Walter Claus, Jared Davis, Joe Deal, Geneva Douglas, Merrill Eisenbud, Asher and Miriam Finkel, Marvin Goldman, James Haggerty, John Healy, Harold Hodge, Ronald Kathren, Harry Kornberg, Sidney Marks, Charles Mays, William Myers, Thomas Noonan, Claire Palmiter, Orr Reynolds, James Robertson, Paul Rohwer, "Van" Romney, Glenn Seaborg, Allyn Seymour, Charles Shilling, Betsy Stover, Robert Thomas, Burt Vaughan, Robert Watters, Ivan White, and Robert Wilson. Some of these supplied

illustrations or other materials as indicated in the captions or text. The ideas and alterations suggested by each of these have been responded to insofar as possible, but this author still assumes responsibility for the final product despite the impressive cadre of people who volunteered to give from a few comments to in-depth reviews and the submission of additional material. As mentioned elsewhere, the author also made considerable use of the historical perspective and files of both Dr. Patricia Durbin and Ronald Kathren.

The manuscript was reviewed in both the Washington, D.C. headquarters of the Department of Energy and at the Richland Operations Office of DOE. Many helpful suggestions were received but no sign whatsoever of an intent to influence content.

The Department of Community and Family Medicine^(a) of the University of California, San Diego, made possible, by a courtesy appointment, entree to the enormous resources of the University of California library system, a campus office and a place to work for the author and for student assistants who helped with the necessary research and kept the author's reprint collection viable. Special thanks go to Mary Catherine Box-Carlsson, who exhibited remarkable abilities to ferret out unusual journals and documents in the formative stages of the work. Benelia Santos helped in the final phases of the project at U.C.S.D.

The primary chore of typing the manuscript and getting it ready for its trip to the word processor was handled competently and, with a serenity that meant much to the author, by Mrs. Barbara Pattinson who worked through R.B. Bookkeeping and later Donald McLean and Co. in Rancho Bernardo. Every word of the manuscript was typed, sometimes many times, by Barbara, who, as a result, knows much more science than she gives herself credit for. Her faithful and effective service over a period of over five years is acknowledged with special thanks.

In addition to the major contributions by Drs. Bair and Baalman at Battelle, described earlier, many individuals in the organization did yeoman duty in preparation for publication. The author is grateful to each of these who participated at one time or another. Special thanks go to Mrs. Grace Miller who handled the chore of obtaining copyright releases.

Finally, but far from least, the author thanks his wife, Grace, for patience and encouragement through the years when BOOK dominated most of the author's working and some of his sleeping hours.

July 1988
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Preface to Chapters on Naturally Occurring Radioactive Elements

We begin this book by considering research on the biomedical aspects of the naturally occurring radioelements. These provided man's introduction to the phenomena of radioactivity and to its effects on living organisms. Indeed, the effects occurred, but were attributed to other causalities, long before the discovery and description of radioactivity at the end of the nineteenth century. Research with understanding akin to our present ideas is largely a product of the twentieth century, with some exceptions.

The work is considered in four chapters, beginning with radium because it was the first radionuclide to be connected with certainty to extensive biomedical effects (even though polonium, a decay-product of radium, was discovered first and contributed to the effects seen).

The discussion of radium concentrates on the use, metabolism, and effects of ^{226}Ra and its daughter products when taken in by the luminous dial painters, radium chemists, and thousands of patients who received radium as a therapeutic nostrum as well as its intake in food and water. The discussion does not consider the long-standing uses of radium as a source of gamma radiation in medicine or the experiences with large radium sources (primarily for the production of radon) in hospitals. The former is a problem of external radiation and thus not pertinent to our theme. The latter involved primarily occupational exposures to health personnel and, while such sources were widespread, documentation of doses, even incidents, is not sufficient to contribute significantly to the story we are unfolding in these chapters. The more recent experience with ^{224}Ra in Germany is summarized also in chapter 1.

Radium is followed by uranium because of the close association between the two, both physically and in the realization of biological action, though the action of uranium is quite different qualitatively and quantitatively from that of radium. The emphasis is on natural uranium, its behavior and effects, with a short discussion of work done on other isotopes.

The third chapter considers the uranium miner saga and related events attributable largely to the effects of radon gas and its daughter products. For pure antiquity, this discussion should come first, for it goes back to at least the

fifteenth century, but the proof of causality came a little bit later than that for either radium or uranium and so did the peak of research activity.

The section concludes with a short review of biomedical research on polonium and on thorium.^(a) As with the others, their presence and potential biological effects were appreciated early, but the crescendo of research built rather more slowly. Also, these were never a focus for as intense activity in the first five to six decades of the twentieth century as was focused on radium, uranium, and, to a lesser extent, radon plus daughters.

It will be realized, of course, that we are speaking very broadly when we name these elements without further elaboration of atomic weight and number. For convenience, we speak generically of "radium," "uranium," "radon + daughters," "polonium," and "thorium." Actually, these titles, of course, encompass groups of isotopes or whole families of elements. The delineation of the several decay series for naturally occurring radioelements was a major accomplishment of the early radiochemists and physicists. Rutherford described the three major series in his Bakerian Lecture in 1904! In toto, there are many dozens of naturally occurring radioactive elements that were isolated, characterized, and related one to another.

The biological research fixed upon a relatively small number of these. Those that assumed prime importance did so because of their abundance, their energies and half-lives, their effects, or all of these. Hence, we can afford to compress the discussion of the biological effects of these substances, which comprised almost all we knew about radioactivity for many decades, into four chapters of modest length.

Before launching into the biomedical aspects and possible health effects of the naturally occurring radionuclides, we must review briefly the major natural series and the miscellaneous primordial radionuclides. There are many ways of presenting these series. Perhaps the most logical is by plots of the atomic mass (A)^(b) or the neutron number (N)^(c) against the atomic number (Z)^(d). The simplest is by a tabulation as was done by Glasstone in his classical *Sourcebook on Atomic Energy* published in 1950 (Glasstone 1950) and in earlier publications.

A more recent version of such a tabulation with updated values for the constants is given in the *Handbook of Radiological Health*, a most useful document for basic physical aspects of all of our discussions in this book (PHS 1970). The three naturally occurring series, beginning with the most important, uranium, and followed by the only slightly less important thorium series, and finally by the actinium series, are shown in tables PN-1 through 3.

It will be noted that many nuclides emit more than one type of radiation per transformation. Many emit such a predominance of one type that they can be represented as decaying by alpha emission, beta emission, etc., on an N - Z plot (see below). Also, note that there are one or more branches in the chains in each series, but again there is a predominant pathway. Finally, it will be noted that the tables give a column for historical names. These are the names that

(a) The story of the health effects of thorium is far shorter than its importance to chemistry, physics, metallurgy, and industry would predict. The reasons will be clear in chapter 4.

(b) Atomic mass (A) is an integer equal to the number of protons and neutrons in the nucleus.

(c) Neutron number (N) is an integer equal to the number of neutrons in the nucleus.

(d) Atomic number (Z) is an integer equal to the number of protons in the nucleus.

TABLE PN-1. Uranium Series Nuclides ($4n + 2$)*

Nuclide	Historical name	Half-life	Major radiation energies (MeV) and intensities†			
			α	β	γ	
$^{238}_{92}\text{U}$	Uranium I	$4.51 \times 10^9\text{y}$	4.15 (25%) 4.20 (75%)	—	—	
\downarrow						
$^{234}_{90}\text{Th}$	Uranium X ₁	24.1d	—	0.103 (21%) 0.193 (79%)	0.063c‡ (3.5%) 0.093c (4%)	
\downarrow						
$^{234\text{Pa}^m}_{91}$	Uranium X ₂	1.17m	—	2.29 (98%)	0.765 (0.30%) 1.001 (0.60%)	
\downarrow						
$^{234\text{Pa}}_{91}$	Uranium Z	6.75h	—	0.53 (66%) 1.13 (13%)	0.100 (50%) 0.70 (24%) 0.90 (70%)	
\downarrow						
$^{234}_{92}\text{U}$	Uranium II	$2.47 \times 10^5\text{y}$	4.72 (28%) 4.77 (72%)	—	0.053 (0.2%)	
\downarrow						
$^{230}_{90}\text{Th}$	Ionium	$8.0 \times 10^4\text{y}$	4.62 (24%) 4.68 (76%)	—	0.068 (0.6%) 0.142 (0.07%)	
\downarrow						
$^{226}_{88}\text{Ra}$	Radium	1602y	4.60 (6%) 4.78 (95%)	—	0.186 (4%)	
\downarrow						
$^{222}_{86}\text{Rn}$	Emanation Radon (Rn)	3.823d	5.49 (100%)	—	0.510 (0.07%)	
\downarrow						
$^{218}_{84}\text{Po}$	Radium A	3.05m	6.00 (~100%)	0.33 (~0.019%)	—	
\downarrow						
$^{214}_{82}\text{Pb}$	Radium B	26.8m	—	0.65 (50%) 0.71 (40%) 0.98 (6%)	0.295 (19%) 0.352 (36%)	
\downarrow						
$^{214}_{85}\text{At}$	Astatine	~2s	6.65 (6%) 6.70 (94%)	?	~0.1%	
\downarrow						
$^{214}_{83}\text{Bi}$	Radium C	19.7m	5.45 (0.012%) 5.51 (0.008%)	1.0 (23%) 1.51 (40%) 3.26 (19%)	0.609 (47%) 1.120 (17%) 1.764 (17%)	
\downarrow						
$^{214}_{84}\text{Po}$	Radium C'	164 μs	7.69 (100%)	—	0.799 (0.014%)	
\downarrow						
$^{214}_{81}\text{Tl}$	Radium C''	1.3m	—	1.3 (25%) 1.9 (56%) 2.3 (19%)	0.296 (80%) 0.795 (100%) 1.31 (21%)	
\downarrow						
$^{210}_{82}\text{Pb}$	Radium D	21y	3.72 (.000002%)	0.016 (85%) 0.061 (15%)	0.047 (4%)	
\downarrow						
$^{210}_{81}\text{Bi}$	Radium E	5.01d	4.65 (.00007%) 4.69 (.00005%)	1.161 (~100%)	—	
\downarrow						
$^{210}_{84}\text{Po}$	Radium F	138.4d	5.305 (100%)	—	0.803 (0.0011%)	
\downarrow						
$^{206}_{81}\text{Tl}$	Radium E''	4.19m	—	1.571 (100%)	—	
\downarrow						
$^{206}_{82}\text{Pb}$	Radium G	Stable	—	—	—	

*This expression describes the mass number of any member in this series, where n is an integer.

Example: $^{206}_{82}\text{Pb}$ ($4n + 2$)..... $4(51) + 2 = 206$

†Intensities refer to percentage of disintegrations of the nuclide itself, not to original parent of series.

‡Complex energy peak which would be incompletely resolved by instruments of moderately low resolving power such as scintillators.

Data taken from: *Table of Isotopes* and USNRDL-TR-602.

Source: Reset from *Radiological Health Handbook*, PHS 1970.

TABLE PN-2. Thorium Series Nuclides (4n)*

Nuclide	Historical name	Half-life	Major radiation energies (MeV) and intensities†			
			α		β	γ
$^{232}_{90}\text{Th}$	Thorium	1.41×10^{10} y	3.95 4.01	(24%) (76%)	—	—
↓ $^{228}_{88}\text{Ra}$	Mesothorium I	6.7y	—	—	0.055 (100%)	—
↓ $^{228}_{89}\text{Ac}$	Mesothorium II	6.13h	—	—	1.18 (35%) 1.75 (12%) 2.09 (12%)	0.34c‡ (15%) 0.908 (25%) 0.96c (20%)
↓ $^{228}_{90}\text{Th}$	Radiothorium	1.910y	5.34 5.43	(28%) (71%)	—	0.084 (1.6%) 0.214 (0.3%)
↓ $^{224}_{86}\text{Ra}$	Thorium X	3.64d	5.45 5.68	(6%) (94%)	—	0.241 (3.7%)
↓ $^{220}_{86}\text{Rn}$	Emanation, Thoron (Tn)	55s	6.29	(100%)	—	0.55 (0.07%)
↓ $^{216}_{84}\text{Po}$	Thorium A	0.15s	6.78	(100%)	—	—
↓ $^{212}_{82}\text{Pb}$	Thorium B	10.64h	—	—	0.346 (81%) 0.586 (14%)	0.239 (47%) 0.300 (3.2%)
↓ $^{212}_{83}\text{Bi}$	Thorium C	60.6m	6.05 6.09	(25%) (10%)	1.55 (5%) 2.26 (55%)	0.040 (2%) 0.727 (7%) 1.620 (1.8%)
↓ $^{212}_{84}\text{Po}$	Thorium C'	304ns	8.78	(100%)	—	—
↓ $^{208}_{81}\text{Tl}$	Thorium C''	3.10m	—	—	1.28 (25%) 1.52 (21%) 1.80 (50%)	0.511 (23%) 0.583 (86%) 0.860 (12%) 2.614 (100%)
↓ $^{208}_{82}\text{Pb}$	Thorium D	Stable	—	—	—	—

*This expression describes the mass number of any member in this series, where n is an integer.

Example: $^{232}_{90}\text{Th}$ (4n).....4(58) = 232

†Intensities refer to percentage of disintegrations of the nuclide itself, not to original parent of series.

‡Complex energy peak which would be incompletely resolved by instruments of moderately low resolving power such as scintillators.

Data taken from: Lederer, C.M., Hollander, J.M., and Perlman, I., *Table of Isotopes* (6th ed.; New York: John Wiley & Sons, Inc., 1967) and Hogan, O. H., Zigman, P. E., and Mackin, J. L., *Beta Spectra* (USNRDL-TR-802 [Washington, D.C.: U.S. Atomic Energy Commission, 1964]).

Source: Reset from *Radiological Health Handbook*, PHS 1970.

TABLE PN-3. Actinium Series Nuclides ($4n + 3$)*

Nuclide	Historical name	Half-life	Major radiation energies (MeV) and intensities†				
			α		β	γ	
$^{235}_{92}\text{U}$	Actinouranium	7.1×10^8 y	4.37 (18%) 4.40 (57%) 4.58c‡ (8%)	—	—	0.143 (11%) 0.185 (54%) 0.204 (5%)	
↓							
$^{231}_{90}\text{Th}$	Uranium Y	25.5h	—	—	0.140 (45%) 0.220 (15%) 0.305 (40%)	0.026 (2%) 0.084c (10%)	
↓							
$^{231}_{91}\text{Pa}$	Protoactinium	3.25×10^4 y	4.95 (22%) 5.01 (24%) 5.02 (23%)	—	—	0.027 (6%) 0.29c (6%)	
↓							
$^{227}_{89}\text{Ac}$	Actinium	21.6y	4.86c (0.18%) 4.95c (1.2%)	0.043 (~99%)	—	0.070 (0.08%)	
↓							
$^{227}_{90}\text{Th}$	Radioactinium	18.2d	5.76 (21%) 5.98 (24%) 6.04 (23%)	—	—	0.050 (8%) 0.237c (15%) 0.31c (8%)	
↓							
$^{223}_{87}\text{Fr}$	Actinium K	22m	5.44 (~0.005%)	1.15 (~100%)	—	0.050 (40%) 0.080 (13%) 0.234 (4%)	
↓							
$^{223}_{88}\text{Ra}$	Actinium X	11.43d	5.61 (26%) 5.71 (54%) 5.75 (9%)	—	—	0.149c (10%) 0.270 (10%) 0.33c (6%)	
↓							
$^{219}_{86}\text{Rn}$	Emanation Actinon (An)	4.0s	6.42 (8%) 6.55 (11%) 6.82 (81%)	—	—	0.272 (9%) 0.401 (5%)	
↓							
$^{215}_{84}\text{Po}$	Actinium A	1.78ms	7.38 (~100%)	0.74 (~0.00023%)	—	—	
↓							
$^{215}_{83}\text{Pb}$	Actinium B	36.1m	—	—	0.29 (1.4%) 0.56 (9.4%) 1.39 (87.5%)	0.405 (3.4%) 0.427 (1.8%) 0.832 (3.4%)	
↓							
$^{215}_{85}\text{At}$	Astatine	~0.1ms	8.01 (~100%)	—	—	—	
↓							
$^{215}_{83}\text{Bi}$	Actinium C	2.15m	6.28 (16%) 6.62 (84%)	0.60 (0.28%)	—	0.351 (14%)	
↓							
$^{215}_{84}\text{Po}$	Actinium C'	0.52s	7.45 (99%)	—	—	0.570 (0.5%) 0.90 (0.5%)	
↓							
$^{207}_{81}\text{Tl}$	Actinium C''	4.79m	—	1.44 (99.8%)	—	0.897 (0.16%)	
↓							
$^{207}_{82}\text{Pb}$	Actinium D	Stable	—	—	—	—	

*This expression describes the mass number of any member in this series, where n is an integer.

Example: $^{207}_{82}\text{Pb}$ ($4n + 3$), ..., $4(51) + 3 = 207$

†Intensities refer to percentage of disintegrations of the nuclide itself, not to original parent of series.

‡Complex energy peak which would be incompletely resolved by instruments of moderately low resolving power such as scintillators.

Data taken from: *Table of Isotopes* and USNRDL-TR-802.

Source: Reset from *Radiological Health Handbook*, PHS 1970.

were applied to individual sources of radioactivity as the series were being worked out and before the nuclides and their interrelationships had been conclusively identified. These names are not used currently but are presented here because they appear in some of the older literature that we will reference. A plot of atomic number (Z) against mass number (A) for the uranium series is given in figure PN-1.

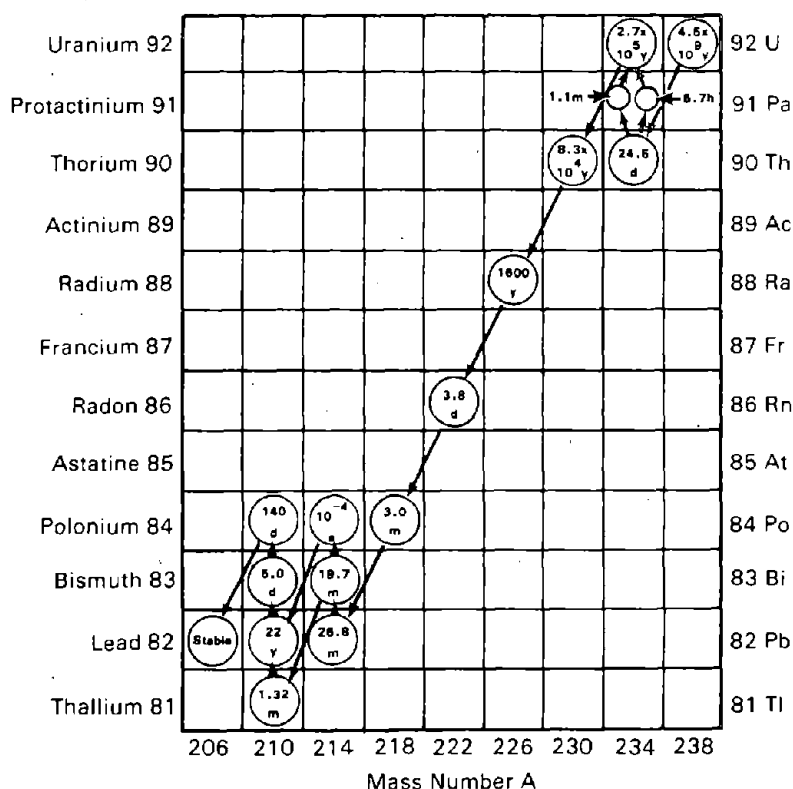


FIGURE PN-1. A Z-A plot of the transitions in the uranium series. (Redrawn from Lapp and Andrews 1972. Reprinted with permission of Prentice-Hall, Inc., Englewood Cliffs, New Jersey, copyright 1972.)

On an N-Z plot, the portion of the uranium series beginning with ^{226}Ra looks as shown in figure PN-2.

Note in figure PN-2 that the predominant radiation emitted in the decay determines the change in N and Z and the position on the plot. Thus, alpha decay shows as a diagonal downward to the left, while beta decay shows as a diagonal downward to the right.^(a)

(a) The actual modes of decay are much more complex than this simple description. There are frequently multiple steps. Descriptions of these can be found in the textbook by Lapp and Andrews (1972) and in general treatises on radioactivity.

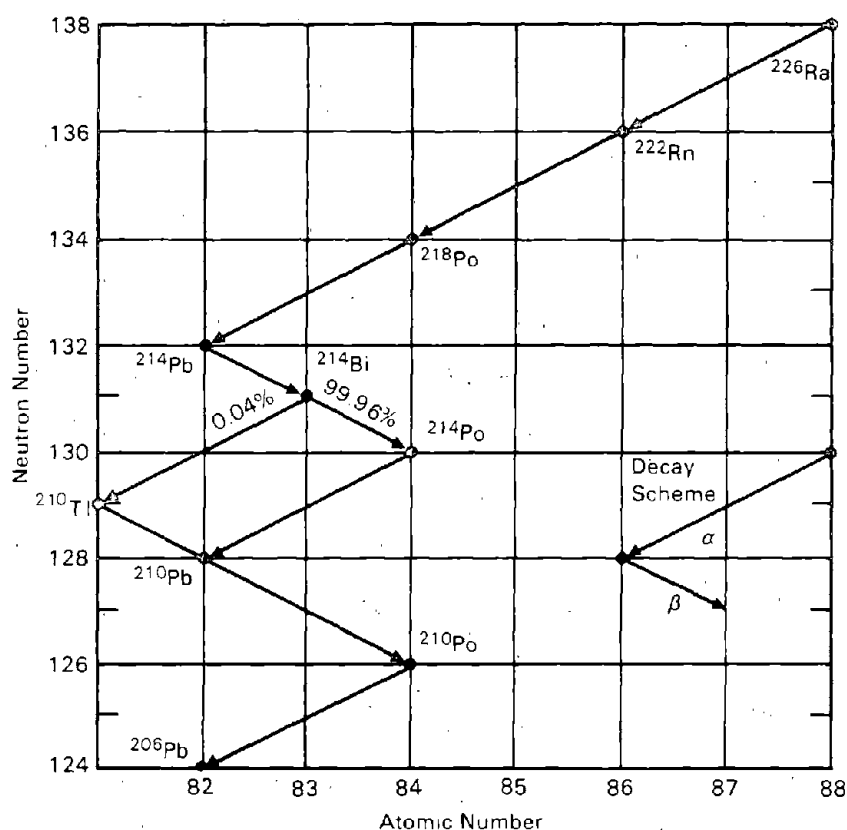


FIGURE PN-2. A portion of the uranium series on an N-Z plot. (Modified from Lapp and Andrews 1972. Reprinted with permission of Prentice-Hall, Inc., Englewood Cliffs, New Jersey, copyright 1972.)

The thorium and actinium series are shown in figure PN-3, again on N-Z plots. Note in these plots and tables that many of the same elements appear in different series, but as different isotopes, and that all three series have a gaseous member, an isotope of radon. In considering biomedical aspects it is sometimes the whole series that is of importance. In other instances, it is only a portion that is of primary interest. Frequently there is a single isotope of significant half-life and energy that is the nuclide of concern. Hence, we will spend much time on ^{226}Ra , ^{224}Ra , ^{210}Po , etc.

The reader will find in the literature still another scheme for representing one or another of the natural series. This is a plot that usually depicts alpha decay as a downward vertical line and beta decay as a diagonal line slanting upward to the right. This plot is convenient and is frequently shown without any coordinate axes. An example, again for the uranium series, is shown as figure PN-4.

It was long appreciated that there should be a series of the type $(4n+1)$, but no indication of the theoretically possible members was found in nature. It was

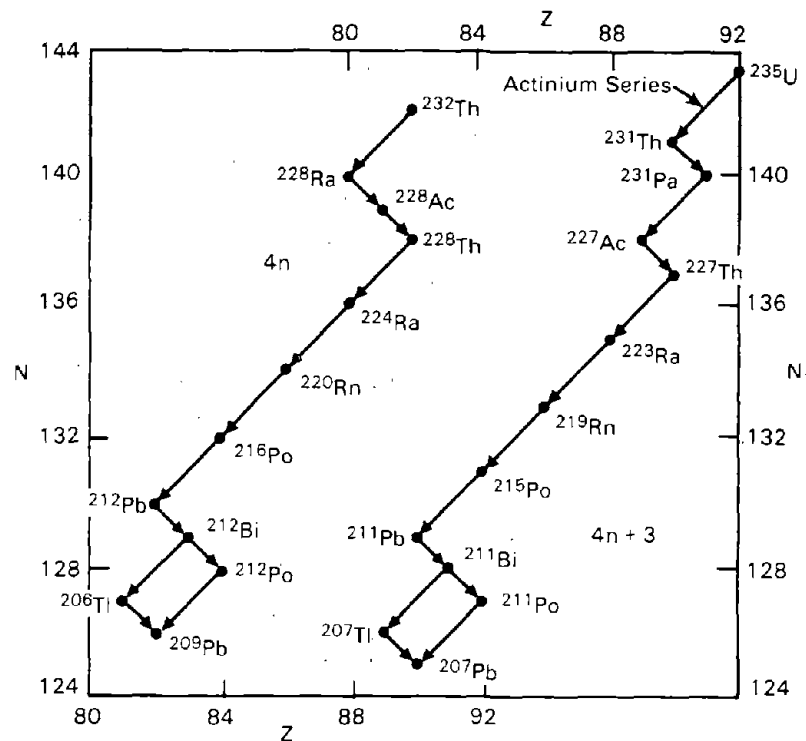


FIGURE PN-3. The thorium ($4n$) and actinium ($4n + 3$) series on N-Z plots. The upper Z scale applies to the actinium series only. (Modified from Lapp and Andrews 1972. Reprinted with permission of Prentice-Hall, Inc., Englewood Cliffs, New Jersey, copyright 1972.)

only after its precursors, ^{241}Pu and ^{241}Am , were produced artificially that its existence and composition were worked out. It begins with ^{237}Np , which has a half-life of 2.1×10^6 yr (and is considered important to radioactive waste disposal). It is thus called the neptunium series. This series on a Z-A plot is shown in figure PN-5.

It will be noted that each of the three naturally occurring series begins with a very long half-life member. This has led to speculation that these may represent primordial radionuclide chains and that there may have been others, indeed the earth may once have been much more radioactive than it now is. These other series may have decayed away and disappeared before they could be detected by man.

In addition to the radionuclides in the several series, there are many other naturally occurring radionuclides that do not seem to be members of any series. The only ones of real interest for biomedical consideration are tritium (^3H) with a half-life of 12.3 yr and a weak beta particle emission; ^{14}C with a half-life of 5,730 yr and a slightly stronger, but still weak, beta particle emission; and ^{40}K with a half-life of 1.3×10^9 yr and a combination beta particle electron capture and gamma emission with energy at 1.5 MeV for the latter.

Many of the other naturally-occurring radionuclides discovered also have very long half-lives and, along with ^{40}K , may be considered primordial. Tritium and

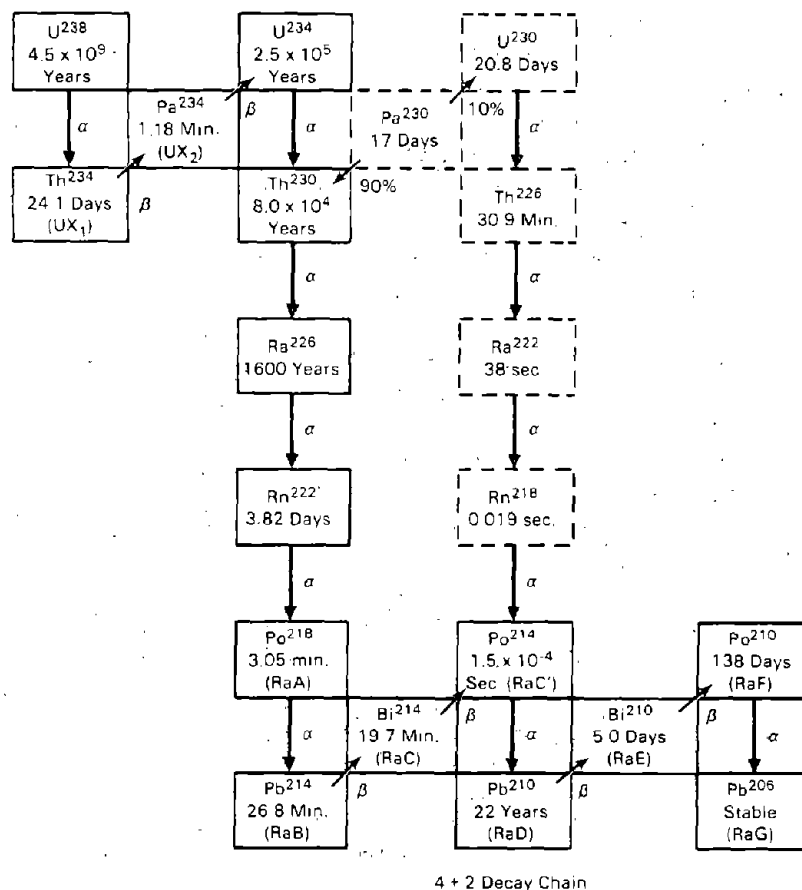


FIGURE PN-4. The uranium series. Note that the series beginning with U^{230} would not occur in nature because of the short half-lives. (Redrawn and modified from Albert 1966, taken from *Thorium Production Technology* by Cuthbert. Reprinted with permission of Addison-Wesley Publishing Co., Inc., Menlo Park, California, copyright 1958.)

^{14}C , by contrast, are constantly renewed by the interaction of cosmic radiation with elements in the atmosphere. Others, such as 7Be and ^{22}Na have such short half-lives that they do not concern us here. A tabulation of the naturally-occurring, "nonseries" radionuclides is shown as table PN-4.

Even though ^{40}K has a low specific activity and comprises only 0.0119% of the earth's potassium, there is so much potassium around that it is estimated to produce the highest mean internal dose rates to the world population from naturally occurring radionuclides. Close seconds are the doses from radon and its decay products inhaled in closed spaces and those from radium and its decay products to the cells lining bone surfaces.^(a)

(a) In this discussion, we are considering only the "internal dose," not the external dose.

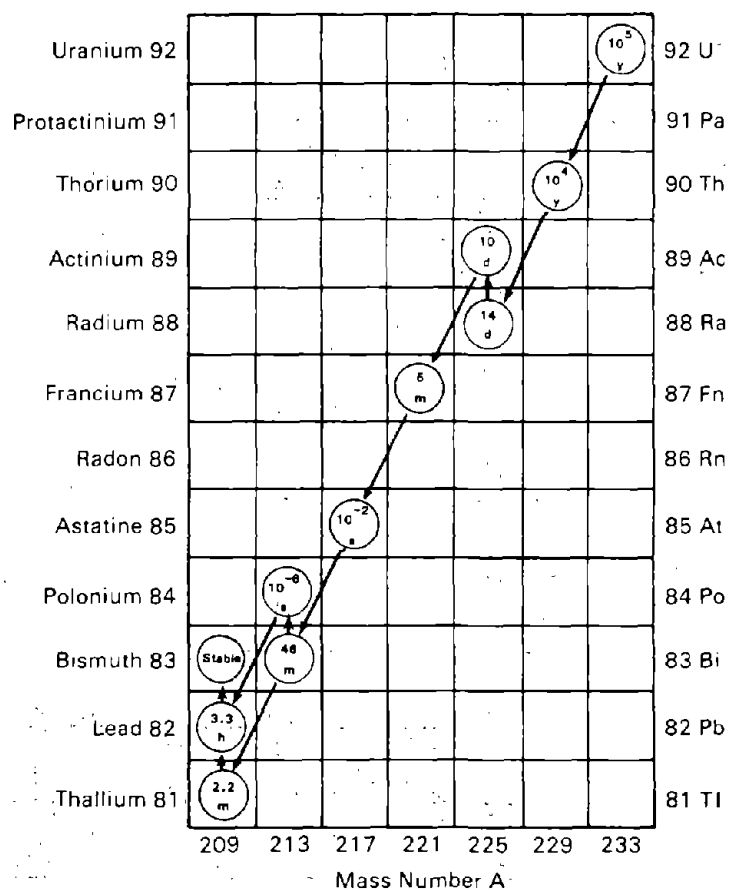


FIGURE PN-5. A Z-A plot of the neptunium series. This series did not exist in nature until its precursors were prepared artificially, but it may have existed on earth millions of years ago. Note that the half-lives except for ^{233}U are very short. Neptunium-237 (half-life 2.14×10^6 years) and ^{233}Pa (half-life 27 days) precede ^{233}U . (Redrawn from Lapp and Andrews 1972. Reprinted with permission of Prentice-Hall, Inc., Englewood Cliffs, New Jersey, copyright 1972.)

A complete and satisfying discussion of the sources and magnitudes of naturally occurring radiations can be found in the reports of the United Nations Scientific Committee on the Effects of Atomic Radiation (e.g., UNSCEAR 1977). (See Appendix D for acronyms and abbreviations.)

In toto, the mean annual dose rate from all natural sources is on the order of 100 to 150 mrem and the dose from internal sources is ordinarily considerably less than the dose from external sources. Such a dose is of little biomedical concern, even though it has sometimes been speculated (incorrectly according to most geneticists) that the natural mutation rate in the biosphere might be primarily due to this background radiation rate.

It was when man began extracting the natural radionuclides from their ores and began to prepare more or less pure compounds or to develop mines that

TABLE PN-4. Naturally Occurring, Nonseries Radioactive Nuclei

Symbol	Nucleus			Percent Abundance	Half-life (years)	Emission	Transition energy (Q)
	Z	N	A				
H	1	2	3		12.3	β^-	0.0186
C	6	8	14		5730	β^-	0.156
K	19	21	40	0.0119	1.3×10^9	β^- , EC, γ	1.5
V	23	27	50	0.25	6×10^{15}	β^- , EC, γ	2.2
Rb	37	50	87	27.8	5×10^{10}	β^-	0.27
In	49	66	115	95.8	6×10^{14}	β^-	0.49
Te	52	78	130	34.5	8×10^{20}	$\beta\beta$?
La	57	81	138	0.09	1×10^{11}	β^- , γ	1.8
Ce	58	84	142	11.1	10^{15}	α	?
Nd	60	84	144	23.9	2.4×10^{15}	α	1.9
Sm	62	85	147	15.1	1×10^{11}	α	2.3
Lu	71	105	176	2.6	3×10^{10}	β^- , γ	1.0
Re	75	112	187		4×10^{10}	β^-	?
Pt	78	114	192	0.78	10^{15}	α	?
Bi	83	126	209	100	2×10^{10}	α	3.1

EC = Electron Capture.
The energies are in MeV.

Source: Reset from Lapp and Andrews 1972. Reprinted with permission of Prentice-Hall, Inc., Englewood Cliffs, New Jersey, copyright 1972.

opened up active sources of radon that troubles from biomedical effects began in earnest. Radium as a component of luminous paint or as a therapeutic nostrum is a typical example. Hard-rock and uranium mining is another. Hence, in these chapters we, in essence, consider the history of the biomedical effects of substances that occur naturally, but that were frequently in more concentrated form than in nature at the time of exposure.

It has become popular in recent years to make a distinction between "natural" and "technologically enhanced" sources of some of the naturally occurring radionuclides. We will have occasion to use this distinction in the chapters considering the environment. In this section, we review the radioelements in the form used at the time of the exposures. On the whole, they have all been "enhanced" to a greater or lesser degree. It is the fact that they originally occurred naturally, i.e., they were not created artificially, and the effects were, in general, first noted before the creation of artificial radioactivity that places them in this section.

For continuity, the work with these radionuclides done over many decades is summarized in each chapter. This includes the period prior to World War II, the work done during the years of the Manhattan Project (Manhattan Engineer District), and in the decades since World War II to the late 1970s or early 1980s. In

later years, the sources may have sometimes included "artificial" modes of generation (for example, the preparation of ^{210}Po); but the properties of the isotopes are identical whether the source was the original natural source or a later artificial process.

For convenience, and again for continuity, most research involving inhalation exposures has been gathered into chapters 9 and 10. This includes the naturally occurring radionuclides. Thus, the chapter on uranium in this section (chapter 2) is considerably shorter than it would have been had all of the enormous efforts on its inhalation toxicology been included. On the other hand, because of its direct bearing on the carcinogenic potential of uranium under long-term exposure conditions, one inhalation experiment, a large one, is included in chapter 2.

The work on radium is continuing, but at a slower pace and with special emphasis on completion of studies on persons exposed many decades ago. This must be done, or much of the epidemiologic value of decades of work will be lost.

Uranium has not commanded the research attention it once got except for waste disposal problems and a belated, but laudable, attempt to mount a formal epidemiologic study of uranium workers. Nevertheless, uranium continues to consume much time and many resources in the realm of industrial operations and regulations.

The most active area at present among these naturally occurring radionuclides concerns radon and its daughter products. The emphasis has shifted away from the uranium mines because of improvements in ventilation (except for continuing litigations regarding past exposures) to exposure of the public. The trend to tighter buildings, for energy conservation, with less air exchange and some unfortunate mistakes in the use of contaminated mill tailings in building materials sparked many investigations in homes and public buildings. The results indicate that radon and its daughters may contribute, even in ordinary buildings, the highest radiation dose to the population of any of the naturally occurring radioelements,^(a) indeed, of all of the radionuclides that deposit in the body under ordinary conditions. Its significance will be discussed at the proper place.

Work on thorium is continuing in the form of epidemiology and continuing efforts to establish true causality in the cases where Thorotrast (a radiopaque dye—see chapter 4) was used. Continuing biomedical work with polonium has been minimal except for attempts to link its presence in cigarette smoke to the development of lung cancer in smokers.

As indicated in the general preface, emphasis has had to be placed in this book on work done in the United States. However, so much of the early basic work on natural radioactivity was done in other countries that these chapters can have more of an international flavor than some other sections of the book.

(a) Radon vies with ^{40}K for this "honor" in populations living in closed dwellings and sometimes wins. In terms of world population, it is not number one because of the large portion of the world population living in open dwellings. Thus, the dose from radon and its daughter products is much more variable than that from ^{40}K . As noted in chapter 4, the tobacco smoker gets a large additional dose from ^{210}Po - ^{210}Pb , but we will not view this as "normal background" radiation to the world population. Recent surveys indicate an additional and sometimes large concentration from the ^{210}Po - ^{210}Pb in foods. These frequently exceed both ^{40}K and radon plus daughters.

Even though current biomedical work with the naturally occurring radionuclides is not today at the almost frenetic pace of some of the earlier decades of this century much continues to be and should be done. In retrospect, we must conclude that the researches on biomedical aspects of naturally occurring radionuclides laid the foundation for the entire field. They continue to make important contributions. The amount that was learned in the early decades, despite crude instrumentation and methodologies that would not be tolerated now because they are too laborious, cannot help but generate much admiration for the scientists and physicians involved.

References

- Albert, R. E. 1966. *Thorium, its industrial hygiene aspects*. New York: Academic Press.
- Glasstone, S. 1950. *Sourcebook on atomic energy*. New York: D. Van Nostrand Company, Inc.
- Lapp, R. E. and H. L. Andrews. 1972. *Nuclear radiation physics*, 4th ed. Englewood Cliffs, N.J.: Prentice-Hall.
- Public Health Service (PHS). 1970. *Radiological health handbook*. Prepared by the U.S. Department of Health Education and Welfare, Public Health Service, Rockville, Md., PB-230 846. Springfield, Va.: U.S. Department of Commerce, National Technical Information Service.
- UNSCEAR. 1977. *Sources and effects of ionizing radiation*. Report of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) to the General Assembly with annexes. Sales No. E.77.IX. 1 Annex B. New York: United Nations.

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Capsule Chronology^(a)

- 1898 Radium-226 isolated from pitchblende by M. Curie.
- 1898 Becquerel receives skin burn from radium carried in his vest pocket.
- 1902 Radium-224 (thorium X) discovered by Soddy and Rutherford.
- 1910 Curie unit defined as activity of 1 g of radium.
- 1910 et seq. Animal work on distribution and excretion of radium (mostly in Europe). Beginning of use of radium as a therapeutic nostrum.
- 1912 Arthritis patient dies because of ^{224}Ra injections.
- World War I Exposure of hundreds of girls to luminous paint compound used for painting numerals on military instruments.
- 1920 et seq. Luminous dial painting expanded to clock factories.
Radium chemists.
Uses of radium by injection and ingestion for treatment of numerous real and fancied disorders increase to thousands of patients throughout decade of the 1920s.
- 1922-1924 Suspicions develop around dial painters' jaw lesions.
- 1924 Description of jaw necrosis by dentist, Blum; attributed to radiation from deposited luminous paint.
- 1925 Physician, Martland, describes pathology of bone changes and anemias in dial painters.
Hoffman decides the dial painters' cases represent a new type of occupational poisoning. Attributes it to mesothorium in dial paint.
- 1925-1929 The saga of dial painters and iatrogenic cases unfolds.
- 1929 Osteogenic sarcoma proven in the dial-painter population. (Reported but not proven to be causally related in 1924 and 1927.)
- 1929, 1930, Collaborative work by Schlundt (Missouri), Failla (Columbia), and
1931, 1933 others on radium metabolism in patients at Elgin State Hospital in Illinois. Patients had received radium as therapeutic nostrum.
- 1931 "Alpha particles are probably the most potent and destructive agent known to science" (Martland).
- 1932 Eben Byers, prominent Pennsylvania industrialist, dies of the effects of drinking "Radithor." Other cases begin to follow. Robley Evans is put on the radium trail by Robert Millikan, and thus begins a brilliant and productive career that continues to this day.
- 1933 First effort to reduce radium body burden by manipulation of diet and administration of parathyroid hormone.

(a) These abbreviated chronologies were prepared as a service to the reader who may wish easy access to the general progression of events or to find a single date. In general, they focus on items described in the text of the pertinent chapters. In some instances, events are listed that could not be included in the text because of space limitations. Also, certain events were pertinent to several chapters. In such cases, the same event is not repeated in several listings unless it has key significance to the subject at hand.

1934 et seq. Principles and practices of in-vivo counting of radium initiated by Evans at MIT.^(a) Continues at MIT until work moves to Argonne National Laboratory in 1970, where it is still continuing; the first "whole-body" counting.

Also much work on the ratio of radon in expired air to radium in the body.

1934-1939 Measurements begun on radium content of natural waters.

1936-1941 More animal work on distribution and excretion and effects of radium and its decay chain products; some of it at MIT. Rat much more resistant to chronic effects of radium than man and not considered a good model.

1941 Standard for radium is promulgated in terms of maximum allowable body burden ($0.1 \mu\text{Ci}$); has held up for decades (see chapter 16). It protected workers during the large expansion of luminous dial painting during World War II.

WORLD WAR II

1941-1947 Examination and measurement of dial painters and patients continues at MIT despite the pressures of war work.

Animal work under the Metallurgical Laboratory (Chicago), partly as "base line" for work with fission products and actinides.

Norris and colleagues demonstrate retention is best described by a power function of time (still referred to as the Norris equation). Soft tissue distributions revealed in depth. Acute toxicity of radium studied in animals. Unique calcification seen in blood vessels and soft tissues. Work on late effects in mice begun by M. Finkel.

Animal work at University of Rochester: distribution and excretion of radium, acute toxicity in the rat, hematology, pathology. Comparative toxicity to plutonium and polonium (Bale, Boyd, Fink, Casarett, and colleagues). Calcification of blood vessels also seen.

POST-WORLD WAR II

1947-1970 Work with dial painters and patients resumes at MIT and increases markedly.

New populations found and added. Dose-response functions determined, idea of practical threshold deduced; osteosarcomas multiply. Carcinoma of the sinuses appears.

1948 Heinz Spiess asked to investigate ^{224}Ra therapy cases in Germany.

1950s Work begins at Rochester (Hursh et al.) on natural radium content of body and of water.

Rochester work on radium during war published as part of National Nuclear Energy Series (Fink).

Role of mesothorium worked out.

Work on man and animals continues at Argonne National Laboratory with special emphasis on patients at Elgin State Hospital.

(a) For abbreviations and acronyms, see Appendix D.

Radium is introduced into the Utah and Davis beagle studies (see chapter 8).

Work at Argonne National Laboratory on areas with high radium content in drinking water.

- Late 1950s through 1960s** "Argonne Radium Studies" (A. Finkel, R. Hasterlik, C. Miller, and others) using new population of dial painters found in Ottawa and La Salle-Peru, Illinois (Argonne National Laboratory and Argonne Cancer Research Hospital).
- 1950s-1970** Large-scale program at Argonne National Laboratory on relative toxicity of radium to many other bone-seeking radionuclides in mice (M. Finkel and colleagues). See chapter 8.
- 1952** Follow-up of ^{224}Ra cases begins.
- 1953** Argonne Cancer Research Hospital opens.
- 1963** Radium-224 added to the Utah beagle experiment.
- 1969** Mays, University of Utah, begins collaborative work with Spiess in Germany on ^{224}Ra cases.
- 1970** Radium work in man consolidated at Argonne National Laboratory in new "Center for Human Radiobiology" with a field station remaining at MIT and a new one in Scottsdale, Arizona, Evans's retirement site.
- Exhumation program continues through all offices.
- Concentration on dose-response functions.
- 1975 et seq.** Follow-up reports on radium patients and female dial workers from Center for Human Radiobiology. Effects and dose-response relationships.
- 1979** Radium-224 cases sufficient for definitive summary.

Chapter 1

First It Was Radium

Overview

This chapter gives a much more extensive coverage of its subject than merely the events between the late 1930s and the mid-1970s as was our original intent. The story of the radium dial painters, chemists, and the nasty surprises that radium brought upon the scene was, I thought, common knowledge among most of the intended readers of this book. But inquiry, both direct and indirect, established that this was not the case, especially among the younger investigators and potential managers who are considered prime targets for this book. Nor was it clear that the extensive past documentation would be read if this chapter began with only a collection of references.

Therefore, at the risk of boring a few readers, I decided to try to cover the whole story to some degree.

The title "First It Was Radium" might be expanded to "First It Was Radium And It Continues To Be." The radium experience has provided the bulk of the original findings on the long-term effects of radioisotopes in the body (internal emitters) and the best source of such information on humans. It continues to provide essential information and, if the projects are continued as they must be, the collection will continue until well into the twenty-first century.

On this basis, the chapter on radium attempts to cover as much of the pertinent research and ideas behind the research as could be mustered without undue length and unnecessary detail. Since the radium saga is basic to all of our other considerations, it is hoped the reader will persevere and find it as fascinating as the author has over the years.

I. Introduction

Why should a book concerned nominally with the organized research on radioisotope (i.e., "internal emitter") toxicology from the 1940s into the 1980s reach back to the end of the nineteenth century to discuss work done so many years ago?

It is because the first extensive experience with the untoward effects of radioisotopes was with radium and its first decay product, ^{222}Rn . It is because the biomedical effects of radium were center stage for much of the earlier twentieth-century work with radionuclides and because experience with radium

has provided the best, most complete, and most reliable information on long-term effects of deposited radionuclides in man. Radium-226 and now some of its shorter-lived cousins continue to supply important bench-mark information. Also, experience with radium provides a total of recorded cases of significant exposure to long-lived radionuclides that exceeds all others. Even the close competitor, exposure to radon and its daughters in mining operations, has not provided as many well-studied and well-documented cases as radium, even though the total numbers of individuals exposed may exceed several fold the total of the radium cases. (The problems of the uranium and other miners will be taken up in chapter 3.)

Was radium really first? It was not in terms of announced discovery. The radioactivity of uranium was announced by Becquerel in 1896 (Becquerel 1896a,b;c, d,e,f). Polonium was the first highly radioactive element separated from pitchblende by the Curies. This was announced on July 18, 1898 (Curie and Curie 1898). The separation of radium waited until December 26 of the same year (Curie, Curie, and Bémont 1898). But in terms of biological effects, ^{226}Ra easily occupies the position of "first" both chronologically and in importance.

The early decades have been extensively documented and provide a chronology second to none in the history of radioisotope toxicology. Nevertheless, we cannot deny ourselves the opportunity to look again, albeit hastily, at that saga. Furthermore, the effort continued throughout the years of World War II and with renewed vigor in the 1960s and 1970s, the periods of most concern to this review. It will continue in the 1980s. The following pages will review first the highlights of the early decades. Then we will look in more detail at the more recent efforts and thereby at some of the biomedical problems still remaining to be solved.

II. The Early Decades

The five years between 1895 and the start of the twentieth century were indeed a remarkable period for radiation science. Beginning with Roentgen's announcement of x rays in 1895 and Becquerel's finding of the radioactivity of uranium in 1896, the period saw in rapid succession the separation of polonium and radium (Curie and Curie 1898; Curie, Curie, and Bémont 1898). Then came the discovery of the radioactivity of thorium announced by Schmidt in 1898, and Marie Curie indicated that thorium ores could be more radioactive than uranium. Further, it was appreciated that these elements had numerous progeny ("daughters") that were also radioactive.

Most of these early activities took place in France and Germany, but they were not alone. In England, J. J. Thomson and his young graduate student Ernest Rutherford were, among others, busy establishing the fundamental physics of "ionization" (Faraday's term). Rutherford established that the radiations emitted by uranium were of two types, alpha and beta he called them. He established the basic properties of and differences between them,^(a) partly after he moved to McGill University in Montreal, Canada.

If it had not been for Irène Curie (as Brucer aptly put it in 1979),^(b) the chronology of the early discoveries in radiation science might have been even more

(a) Others cite Pierre Curie as doing this separation and classification in 1900.

(b) American research on radioactivity in the early twentieth century is beautifully summarized and analyzed in a recent book by Badash (1979).

closely packed. It was hardly Irène Curie's fault, but her gestation period happened to come right in the period of feverish efforts by her mother to separate out the unknown sources of radiation coming from uranium ore. In retrospect, it may have been just as well that her fetal development took place before her mother had been unduly exposed to radiation as she undoubtedly was as the work progressed. For, as we shall see in chapter 5, Irène Curie followed fittingly in her mother's footsteps and brought forth, with her husband Frédéric Joliot, the first artificially produced radioisotopes.

The biological effects of radiations from radioisotopes were not long in coming to light. During the first months after the announcement of the properties of uranium and radium, Becquerel is reported to have carried a small vial of radium, obtained from Madam Curie, in his vest pocket in order to demonstrate its remarkable properties on short notice. It is further reported that Becquerel turned up with a classic erythema (from a radiation burn) on the skin next to his vest pocket. This was, of course, an effect of the penetrating radiation from the radium. It was *not* an effect of a radioisotope deposited within the body. But we can put it down as the first recorded effect of the radiations from radium.

The history of the discovery of biomedical effects of *deposited* radionuclides is quite different from that of x rays and external radiation sources in general. It was less than a year from the beginning of the general use of x rays that untoward biological effects were recognized. The better part of two decades passed before similar appreciation came regarding radionuclides deposited in the body. This situation was due in part to the relatively fewer chances for exposure because the sources were usually encapsulated, and only their penetrating radiations were employed in medicine. It also reflects one of the most characteristic features of internal emitter toxicology. Except for occasional large exposures, we are dealing with effects that have years of latency before the end result becomes apparent, "the slow burn" in modern parlance. In addition, there seems to have been something of a blind spot in the thinking of those years, and the possibility of catastrophic long-term effects of deposited radionuclides, especially alpha emitters, seems not to have been brought into focus. There was animal work from about 1910 on the distribution and excretion of radium (see bibliography by Schwind and Croxton 1950). But it was into the post-World-War-I years before the biomedical effects came suddenly to light, and the toxicity of radium in the body became fully apparent. And the results are still accumulating (1980s)!

III. Luminous Dial Painters, Radium Patients, etc.: The First Decade of Enlightenment

As Eisenbud (1979) remarked, an extraordinary series of coincidences, plus some prepared minds, resulted in a sudden and rude awakening to the effects of alpha emitters deposited in the body. It began in 1924 with a perceptive dentist (Blum), followed quickly by a conscientious and talented physician and pathologist (Martland), a chemist (Gettler), another perceptive physician (Hoffman), and later a remarkable series of measurements, analyses, and interpretations by a capable and broad-gauged physicist (Evanis).

The prodromal signs were already present in what was termed at the time "professional anemias," which occurred in radiologists and others using x rays

and radioactive materials in medicine (Martland, Conlon, and Knaf 1925, p. 1786). But the fat was not fully in the fire until a New York dentist, Theodore Blum, mentioned an entity he termed "radium jaw" in a three-line footnote to a paper given before the American Dental Association on osteomyelitis of the jaw (Blum 1924). Blum was impressed by the unusual and intractable nature of the osteomyelitis in a girl from New Jersey who worked in a dial-painting plant. Other cases of jaw necrosis were being seen by other dentists.

In 1925, F. L. Hoffman was called to the plant by the New Jersey Consumers' League.^(a) He was impressed by the similarity of the death certificates of deceased former employees and decided that they represented a new type of occupational poisoning. He attributed it to mesothorium in the luminous dial paint (Hoffman 1925). This report was followed very shortly by the paper by Martland and colleagues already cited. Martland was with the medical service of St. Mary's Hospital, Orange, New Jersey, the pathology department of City Hospital, Newark, New Jersey, and was, in addition, in the office of the county physician of Essex County.

The picture was one of acute necrosis of the jaw, usually involving infection and severe leukopenia and anemia, occurring from one to seven years after the patients terminated work as dial painters. (Many of the young women worked at dial painting during World War I.) These are what would now be characterized as "early cases" (Martland 1929). The causative agents were identified as ^{226}Ra , and/or mesothorium, primarily mesothorium I, an isotope of ^{228}Ra , with a leaning toward implicating the latter.

There were, of course, the usual protestations of innocence on the part of the company. It was not the paint but something else, even syphilis. Even some quite sincere physician-investigators, e.g., F. B. Flinn, required three or more reports, each one incorporating new evidence, to be fully convinced.^(b) (Perhaps this was because Flinn was seeing women from the watch- and clock-making plants in Connecticut, and the paint did not have the same composition there.)

The factory executives commissioned their own investigation as to whether or not any occupational hazard existed. A report was prepared by W. B. Castle, Katherine R. Drinker, and Cecil K. Drinker of Harvard University in March 1924 (Castle, Drinker, and Drinker 1925). It seems not to have been at variance with the Martland or Hoffman reports in implicating alpha radiation from deposited radium, but it was delayed in publication at the request of the company because of threatened litigation and also to give time to check up on evidence for possible zinc poisoning and the possible role of general hygiene in the plants.

The first patients examined carefully enough to provide full details, including autopsy samples for both pathological and radiochemical analysis, were those

(a) This was part of an organization, the National Consumer's League, that has a venerable history of crusading for causes of worker health and rights. Erma Angevine (1979) has prepared a definitive history of the League. Among those active on the dial painters' behalf was Florence Kelley, a protégé of Alice Hamilton, whose efforts have been described recently by Roger Cloutier (1979, 1980). Both of these papers introduce the sociological and economic aspects of many of the events that we will review in this book from the standpoint of scientific research and discussion of which we must forego in order to tell the scientific and technical history.

(b) The completeness of Flinn's conversion to the view that radium was the culprit is attested to in a later paper, "Stimulating Action of Radioactive Deposits in the Body," published in 1934 (Flinn 1934).

reported by Martland (1925). In inexorable progression the saga unfolded. Probably the clearest, most-detailed presentation of both historical order and medical characterization can be found in Martland's later review paper (Martland 1929). The fact that a new occupational hazard was upon us was gradually accepted. Indeed the dial-painting plants were modified and cleaned up, and the practice of tipping the brush between the lips was prohibited so that further exposures from this source probably ceased by the late 1920s. Some put the date as early as 1926.

Cases showing less serious effects began to appear. These presented a somewhat different clinical picture, less necrosis, less anemia, less disability. It was thought that these individuals had less total body burden or the mesothorium had decayed away (5.7 years half-time) without exerting its effect as fully as in cases with more mesothorium. The anemia, if it persisted, was of the regenerative type. Toward the end of 1928, Martland hoped that the worst period, at least for the New Jersey cases, was over.

But it was, as Martland states, "an insidious lull." By the end of 1929, cases of osteogenic sarcoma began to appear, with the death of one young woman.^(a) Pathologic fractures began to appear also, and it was clear that a second, more insidious, but just as serious, stage had begun. Actually, bone sarcomas were reported from two cases dying in 1924 and 1927 (Martland and Humphries 1929), and these led Martland to suspect that there would be more to come. Indeed, he stated in 1929 that in 1925 he made a list of fifty out of the eight hundred or so women employed at the New Jersey plant most likely to show symptoms using length of employment as the criterion. "With terrible, almost mathematical regularity, I have been crossing off these names as the girls have died or developed symptoms of radium poisoning."

The late cases had many differences from the early ones. These differences included in some cases fairly long periods of reasonably good health that continued up to a few months before appearance of the terminal cancer. Also, there were many puzzling exceptions noted, including some differences occasioned, it would appear, by differences in the paint at different times and at different plants. Many of these will be examined when we look at the more analytical decades to follow in later sections.

Despite the furor stirred up by the luminous dial painter cases, exposure to radium continued to occur elsewhere during all of the 1920s. Chemists, physicists, and physicians working with radium were among those fatally exposed. The chemist who mixed the paint for the New Jersey plant, doing it only himself because it was a trade secret, was one of them. But they were a heterogeneous group scattered about the country and did not attract the kind of attention a group of eight hundred girls and women could.^(b) Also, practitioners of medicine continued to give injections of radium for its "stimulative action."^(c) Many

(a) She was one of five who had been given an out-of-court settlement for their disabilities, inadequate of course, and the press picked up the issue under the rubric of *The Five Women Doomed to Die*.

(b) There were many other dial-painting plants and some hundreds of other dial painters, but their story took much longer to unfold. In fact, the more complete version has had to wait until the post-World-War-II years, as we shall see later in this chapter.

(c) These are termed in the literature "iatrogenic" (Greek, *iatros*, physician + -GENIC for generated). One wonders what therapy is now in use that will have effects that some future generation will label "iatrogenic."

patients drank radium water or a patent nostrum called "Radithor," sometimes in quantities that stimulate admiration for the resiliency of the human machine. The harvest was slower to be reaped (or was it slower to be recognized?) in these cases than in the worst of the dial-painter cases.

IV. The Decade of the 1930s: Quantitation, Therapy, and Metabolism

A. The Transition

While the publications on radium in humans in the 1920s were laced with discussions of possible mechanisms of the pathologic changes seen, some of them very complete (e.g., Martland 1929), the primary lesson of the decade of the 1920s might be summed up in Martland's conclusion: "Alpha particles are probably the most potent and destructive agent known to science." There had been pioneering research efforts on retention and distribution, e.g., as a function of route of administration (Seil, Viol, and Gordon 1915; see also survey by Silberstein 1945, 1950a; and bibliography by Schwind and Croxton 1950), and some quite prescient discussions of how radium is metabolized, i.e., like calcium and like lead. Nevertheless, the latter part of the 1920s and the decade of the 1930s, up to the time of our entry into World War II, saw a marked increase in such investigations. These were aimed primarily at quantifying the radium burden of people exposed in earlier years, at establishing the kinetics of distribution in and clearance from the body, and, in general, getting at the mechanisms behind the events established in the 1920s.

Since the decade of the 1930s saw the beginning of the work of Robley D. Evans, who has been, and is, a towering figure in the field of radium toxicology (indeed all of radiation toxicology), we might well start with his introduction to the field. Evans is a physicist with profound interest in and understanding of biology. Throughout his career, he has been part of singularly symbiotic associations of physicians, dentists, physicists, chemists, biologists, even epidemiologists, where no one lost his identity, but the whole has been much more than the sum of its parts. The way he got "invited" into the radium field is interesting and worth repeating, for he was doing Simon-pure physics and geophysics at the time, related to radioactivity from natural sources.

In 1932, a prominent Pennsylvania business tycoon named Eben Byers, president of Byers Steel, died from the effects of slavish devotion to the nostrum "Radithor." Radithor was certified to contain 1 μCi of ^{226}Ra and 1 μCi of ^{228}Ra (radiothorium) per half-ounce bottle. Mr. Byers had devotedly taken four bottles per day for a considerable period! It perhaps did have the often described initial stimulatory effect of radiation and radium, but it brought Mr. Byers down with classic radium poisoning.^(a)

Perhaps it was because Mr. Byers was National Amateur Golf Champion, as well as a very popular bachelor and well-known industrialist, but, for whatever

(a) Only the well-to-do could afford four bottles of Radithor per day. It took somewhat longer for ordinary folks, but they got there just the same. The number of persons who took radium in one form or another on either their own initiative or through their physicians will never be known accurately. But the total is bound to be in the thousands.

reason, his death brought spreads in the national press, including a relatively new magazine called *Time* (Evans 1978a). The Los Angeles County Health Department recoiled at the idea that such things might happen in California. They sent an emissary to Robert Millikan, well-known physicist at Cal Tech, and Evans's boss and thesis advisor. Millikan brought the representative (a Dr. Crandall) to Evans with some remarks to the effect that here was a man interested in radium and left him with the remark, "you do what this man tells you." Thus, by a fortunate accident began one of the longest and most productive careers in American radiation science and the toxicology of deposited radionuclides.

The first tangible result of this assignment was a paper by Evans before the American Public Health Association, published in 1933, by which time Evans had become a National Research Council Fellow at the University of California, Berkeley (Evans 1933). The paper is a carefully structured review of the work already done, some of it only begun, and it presaged many areas that were to occupy his attention and that of many others in the years to come.^(a)

B. Measurement In Vivo

A central theme of Evans's work, and much of that in the period, was the quantitative measurement of body burden of radium and related nuclides in living individuals. The work in the 1920s included measurements of expired radon and thoron, more as a clue to whether or not a given case had a significant burden than as a quantitative measure. Also, measurements were made by placing electroscopes near the individual and also by analysis of feces. (Since exposure was largely by ingestion, urinary excretion was negligible.) The results were far from satisfactorily quantitative. Evans began studies on the metabolism of radium in patients in 1933 (Evans 1978b). However, the primary thrust toward measurements in vivo awaited his joining the faculty of the Massachusetts Institute of Technology (MIT) in 1934.

The techniques developed at MIT used Geiger-Müller counters (gamma-ray quantum counters) to measure the relatively feeble gamma emissions from deposited radium C in the human body (Evans 1937). They differed from earlier measurements that used gamma-ray electroscopes and which required obtaining autopsy samples of bone for calibration (see Schlundt, Barker, and Flinn 1929; Barker and Schlundt 1930). They were susceptible to internal calibration by a method known as the "Meter Arc Calibration Technique." The principle is that the patient is located so that all portions of his body lie on an arc with a 1-m radius to the detector, which is at the center. By measuring with the patient first facing the detector, then with the back toward the detector, remeasuring with known radium standards placed behind the shoulders, hips, and knees, and finally measuring with only the standards present, a calibration could be made. Not many patients were subjected to this time-consuming process, and some had to be along a 1.5-m rather than a 1-m arc. But the procedure gave calibration points so that routine measurements could be made away from the laboratory with the patient seated in a chair, and the detector could "look at" eleven points 1 m away.

(a) In Evans's case, these were side by side with continued work in physics, instrumentation, and geophysics, and a major text on the atomic nucleus.

This was essentially the beginning of whole-body counting, and it happened in the early 1930s!

The technique was supplemented by analyses of expired radon. This procedure was carried out for two purposes: (1) Many patients and workers could not be brought to the laboratory, but breath samples could be collected and measured, and (2) calculations of radiation dose depended critically upon quantitation of the fractional loss of radon from individuals bearing a measured radium burden.

With gradually increased sensitivity and sophistication of instrumentation, the measurement of the gamma emissions from deposited radium continued for a variety of individuals grouped under the general heading, "The MIT Cases," or sometimes the "MIT-MGH Cases." In the earlier days, those measured were primarily those referred by physicians to the Massachusetts General Hospital (MGH) or perhaps directly to the laboratory because they either had symptoms, or they themselves suspected they had a body burden of radium or luminous dial compounds. Later the investigators began to seek out individuals expected from the records to be bearing radium or luminous compounds. Indeed, it is reported that a private detective was hired at one point in the study to help trace down some of the dial painters who had married, moved many times, and might or might not place any importance on their period of employment as a dial painter.^(a)

Concurrent with the developments at MIT-MGH was a collaborative effort by Herman Schlundt, a physical chemist at the University of Missouri; Howard H. Barker of the U.S. Radium Corporation; Frederick B. Flinn, M.D., a professor at the Institute of Public Health at Columbia University; G. Failla, a radiological physicist at Columbia; and later, John T. Nerancy, M.D., Clinical Director at the Elgin State Hospital, Elgin, Illinois. In a series of papers under the general title, "Detection and Estimation of Radium in Living Persons," these workers wrote first about the methods themselves (Schlundt, Barker, and Flinn 1929), the estimates of body content of ten patients treated with radium (Barker and Schlundt 1930), the normal elimination of radium from living persons (Schlundt and Failla 1931), and the first reports from the Elgin State Hospital group of patients (Schlundt, Nerancy, and Morris 1933). This research centered primarily on measurements of amounts present and the "metabolism" of radium rather than upon effects. It is notable, in part, for uncovering the relatively large and stable group of cases given radium injections iatrogenically in the Elgin State Hospital. But the primary contributions of these cases had to await the Argonne Radium Studies begun in the early 1950s. (See post-World-War-II work.)

(a) Exaggerated and totally incorrect rumors seem to have dogged radiation science from the earliest days. One such refers to Evans's measurements of the radium burden. Dr. Samuel Lind, one-time president of the American Chemical Society, spent much of his professional career on the properties of alpha-particle-emitting elements. Suspecting that he might be carrying a significant body burden, he checked in at Evans's laboratory to be measured. Later he partook of a friendly dinner at the Evans's house. Much later, a rumor appeared that Evans had surreptitiously placed a gamma-ray counter under Lind's chair at the dinner table and had the counting equipment set up in the kitchen. Evans's frequent trips to the kitchen were put down as trips to take readings. Totally untrue! No one knows how the story got started. Having also had dinner at the Evans's home, I suspect his frequent trips to the kitchen were to refill his guests' wine glasses, or otherwise see to their needs.

There were studies and measurements of dial painters in England and in Switzerland where farm wives did dial painting during the winter months. Also in this period there grew a sizeable French literature, primarily on metabolism and effects, but well quantified; and much work was done in Germany, particularly in the laboratories of Rajewsky and Krebs (see Silberstein 1945, 1950a). Some of these will be cited in other connections. Others must be omitted.

On balance, it was the MIT-MGH group that kept consistently and systematically at the business of measuring radium body burdens during the 1930s. And in those days, it was primarily radium rather than mesothorium that could be measured *in vivo*. It was slow work, however. By the early 1940s, a total of twenty-seven cases had been studied in enough detail to be the basis for the radium exposure standard, which will be taken up in chapter 16.

C. Approaches to Therapy

The gradual realization that there were many hundreds of human beings with body burdens of radium and luminous paint compound that portended serious illness in their later years naturally led to investigation into possible means to remove the deposited radium. A process of "deleading" patients suffering from lead poisoning was proposed by Aub et al. at MGH in 1926 (see Aub et al. 1926). Since lead acted much like calcium, and radium was metabolized much like calcium, it was decided to try to influence first lead and then radium with agents that affected calcium metabolism and by manipulation of calcium intake in the diet. These were the days when "viosterol," a vitamin D preparation, was used in large quantities. It was, of course, a logical candidate for possible therapy because of the important role of vitamin D in calcium metabolism. Another candidate was parathyroid extract (Hunter and Aub 1927).

The pioneering work toward therapy of radium poisoning was done by Flinn and Seidlin (1929) using parathyroid hormone and by Flinn (1931) using viosterol. Later, Craver and Schlundt (1935) introduced low- and high-calcium diets along with parathyroid hormone (extract) and viosterol. There seemed to be some increase of radium excretion with low-calcium diet plus parathyroid extract, but there was no substantial reduction of the total amount of radium in the body.

The MIT-MGH group joined the activity with a study of three patients (Aub et al. 1938). They used manipulation of calcium intake and parathyroid extracts and other measures such as ammonium chloride, magnesium gluconate, and thyroid extract. The quantities of radium mobilized were enough to increase elimination significantly (excreta were routinely collected and analyzed in this work), but the effect on total body burden of radium was still small. Yet, in one case, there was marked clinical improvement, particularly of the jaw symptoms and roentgenographic changes.

On the whole, it appears that these forays into therapy did more to enhance knowledge of radium metabolism than to provide a truly effective therapeutic tool. It is not surprising that mobilization of large amounts of radium did not occur. Experience in later work with a variety of nuclides to be discussed in chapter 19 indicates that the heavy metals once fixed in bone are difficult to remove, and even when removed from bone may still be difficult to transfer from blood to excreta. Also, there are strict limitations on what can be done without risking serious imbalances of calcium metabolism because calcium seems to be more mobile than the heavy metals.

The number of cases studied was of course small. The facilities of a fully equipped metabolism ward were needed, and the work was expensive and demanding. Whether due to differences in the state of radium in the body or other factors, the results were quantitatively quite disparate. This fact, plus the small number of cases studied, left for posterity an equivocal story that rates "A" for effort but which did not encourage further large investments of time, manpower, and money.^(a)

D. Distribution, Excretion, and Retention of Radium

Definitive information on the "metabolism" of radium was slower in coming than the clinical findings and the facts of radium poisoning. This situation was due in large part to the fact that the actual intake was not quantified except in retrospect by the work from the Schlundt group and the Evans group already described. Good metabolism studies require a reasonable knowledge of the initial dose and the initial body burden upon which subsequent behavior can be based. The bibliographies by Silberstein (1945, 1950a) and by Schwind and Croxton (1950) contain references to deposition in animals, including horses, as far back as 1910 and in humans during the 1920s, e.g., Schlundt, Barker, and Flinn (1929), but satisfactorily quantitative work began in earnest during the 1930s. Information from humans and from rats appeared almost simultaneously in 1933. Schlundt, Nerancy, and Morris (1933) utilized the group of patients at the Elgin State Hospital, Elgin, Illinois. These patients received weekly doses of about 10 μg of ^{226}Ra over periods of two to ten months in 1931. The doses were intravenous and reasonably well known except for the ubiquitous problem of adherence of the nuclide to the inside of syringes, bottles, etc. They were given as something of a last spurt in the use of radium injections for therapy in reputable medical institutions. The authors measured exhaled radon and gamma-ray emission from the patient's back.

Thomas and Bruner (1933) gave ten albino rats injections of 5 μg at irregular intervals. While the main thrust of their study was to check effects for comparison with those seen in the dial painters (they were qualitatively similar except for the anemias), they analyzed the residual carcasses of eight experimental animals with considerable care.

The results of both these studies and others (see summaries already cited) showed that radium was eliminated fairly rapidly after entry into the body, with elimination largely via the feces. There was deposition initially in many soft tissues including kidney, liver, spleen, and bone marrow, but retention was short in these, whereas bone accumulated larger and larger fractions with time. Thus, for consideration of long-term effects, it could be assumed that 90% or more of the radium was in the skeleton. (There was an effect of route of administration, however, with much less remaining in bone after intradermal administration [Silberstein 1950a]). Furthermore, the skeletal distribution itself was far from uniform. Different bones concentrated different amounts, and within a given bone there were marked differences. In general, the growing epiphyses localized radium rather specifically, perhaps in part because of their rich blood supply and in part because new bone growth was occurring there. But at later

(a) It is puzzling, however, that radium seems not to have been a prime candidate for study when the various chelating agents came along in later years (see discussion in chapter 19).

times, the radium was seen to migrate into the mineral phases—presumably by exchange for calcium. In this form, the radium is most difficult to remove, which may account for the poor results of attempts at therapy. Thus, although only a small fraction of the initial dose was retained, that fraction was very firmly bound, and retention half-times of forty years or more were estimated even in these early studies. Finally, it appeared that oral doses were eliminated more readily and more completely than parenteral doses.

Details of the metabolism of radium in humans and animals have occupied the attention of investigators ever since. We will have occasion to look again at this subject as we examine the work of later years. We should pause, however, to note that even this early work was quite useful, and in some respects it set the stage for much of the work on retention, distribution, and excretion, which became central themes of the internal emitter toxicology programs of World War II and beyond. Conversely, the radium studies took their cue from toxicological work with nonradioactive heavy metals conducted in many of the same institutions.

The importance of knowing what fraction of the radon produced from decay of radium in the body was exhaled has been mentioned. This figure is crucial to dosimetry since it determines the amount of energy imparted *in vivo* by all of the daughter chain. A single figure is used, the one associated with long-term retention. Figure 1.1 is a graph reproduced from Silberstein's review (p. 19); it

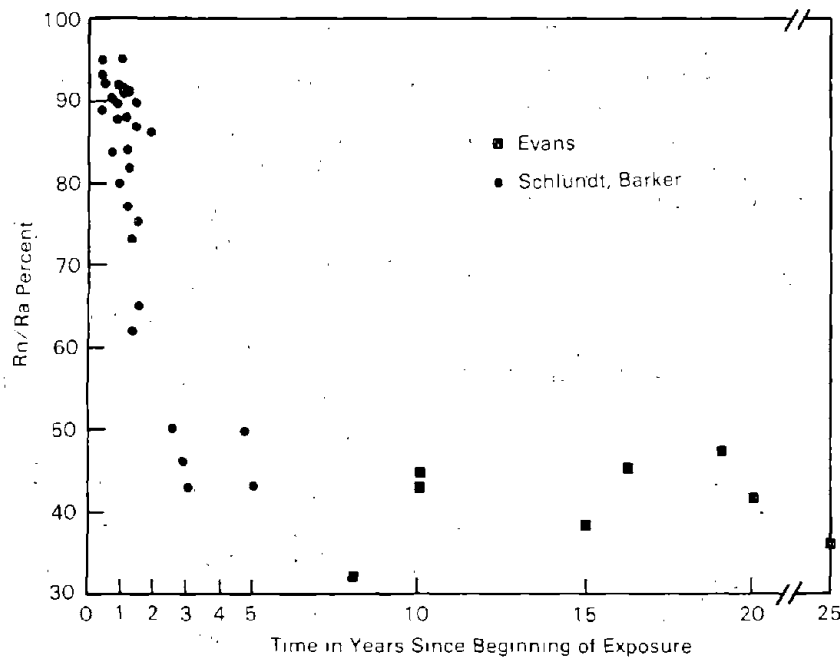


FIGURE 1.1. Relation of expired radon/total radium to retention time in man. (Redrawn from Silberstein 1945, p. 19. Solid squares represent consolidated data from Aub et al. 1938; and Evans, Harris, and Bunker 1944. Solid circles represent consolidated data from Barker and Schlundt 1930; Schlundt and Failla 1931; Schlundt, Nerancy, and Morris 1933.)

shows that this fraction is far from stable during the first three years. Most of the data shown in figure 1.1 were gathered during the years we have been examining in this section. While details have changed since, I submit this is not bad for what some might regard as "very old" work.

V. Radium Research During World War II

A. Introductory Considerations

It could be conjectured that research with radium would have been greatly reduced, even discontinued, during the years of the Manhattan Project (Manhattan Engineer District, [MED]). After all, there was a large backlog of information on radium, and tremendous efforts were needed on the new problems of the fission products, uranium, and the transuranic elements, the rare earths, and others to be discussed in later chapters. In fact, however, there was considerable additional work with radium. True, it was less emphasized than in the previous two decades, and, in contrast to the feverish activity surrounding the new problems, it was done at a relatively slow pace. The radium work, for example, is hardly mentioned in the monthly reports of the Plutonium Project or other internal documents of the MED.

The logic behind continuation of radium research by the MED lay in the following:

1. Radium-226 was the standard to which many of the new elements had to be compared. Many animal experiments were necessary to learn of the metabolism and toxicity of these new elements. Because of possible species differences, it was deemed advisable to run "control" groups with ^{226}Ra to anchor the new studies to an element we knew something about.
2. The dose-response relationship for radium needed filling-in over a wider range of doses.
3. The effects of fairly high doses needed quantitation because acute exposures to the new elements were considered possible and were being studied in animals.
4. Patients and workers with radium burdens from earlier exposures continued to appear and required both measurement and attention. The continuity of the measurements of body burden and clinical condition could not be broken without threatening most of the previous investment.
5. Many aspects of distribution and retention required more quantitative information.
6. The Armed Services, particularly the U.S. Navy, with requirements for thousands of luminous dials to be painted, wanted to be sure there was no repeat of the exposures during World War I. To this end, they insisted on having an authoritative standard for radium exposure and body burden. We will return to this in chapter 16.

The research with ^{226}Ra in the Manhattan Project was concentrated at two installations, The Metallurgical Laboratory, primarily workers in Chicago, and the project at the University of Rochester Medical School, Rochester, New York. In addition, there was indirect and some nongovernmental support for the continuation of the MIT-MGH work in Boston and Cambridge, Massachusetts, although these laboratories were not officially part of the biomedical effort of

the MED. There was also some anchor-type work done with radium in the University of California, Berkeley, portion of the Metallurgical Laboratory, but this was primarily for range finding.

The wisdom and foresight of Dr. Robert S. Stone, General Medical Director of the Metallurgical Laboratory, must be recognized for providing continuity to the accumulated information on radium and the addition of needed new data.

B. The Chicago Work on Radium-226

Two groups of workers at Chicago can be identified. One, associated primarily with William P. Norris and his colleagues, considered primarily metabolism and toxicity, and under the aegis of Leon Jacobson; hematological effects. The other considered largely longer-term toxicity, particularly carcinogenesis and life-span shortening, and is associated primarily with Miriam Finkel for the experimental work with mice and Austin Brues for some early animal work, later human work, and a general interpretative and philosophical role as a laboratory administrator.^(a)

The work of Norris and Evans (1946) and Jacobson and Simmons (1946) appeared first in Project Reports. Since these papers were never published in their entirety in the open literature,^(b) they will be reviewed in some detail.

The studies by Norris and colleagues involved the toxicity of radium in mice and rats and excretion and retention in mice, rats, and rabbits. The injection route was intraperitoneal or intravenous and the dosages from a little over $2 \mu\text{Ci/g}$ to $0.02 \mu\text{Ci/g}$. The injected radium was metabolized very rapidly. By only two minutes after intravenous injection, less than 10% of the radium could be found in the circulating blood. After intraperitoneal administration, the blood concentration increased rapidly to about 4% of the injected dose, then decreased rapidly. Clearance from the peritoneal cavity was complete within one hour.

There was transient concentration of radium in soft tissues, but only bone retained the element for any extended period. Excretion was rapid, more than 50% of the total occurring within twenty-four hours, with, in the case of the rats, about 60% in feces, 40% in urine. By ten days after administration, excretion attained a very low rate that was maintained thenceforth. Norris found that the early excretion rates could be represented by a linear function plotting $\log E$ (excretion as percent of injected dose per day) against time expressed as $\log T$. The loss function was as the -1.5 power of time for total excretion in the mouse and for urine and feces from the rat, data plotted separately.

Of particular interest is the fact that in all species the retention of radium increased with increasing dose level. This too was related linearly when $\log R$ (percent retention) was plotted against dose level ($\log I$). But the slopes of the lines were different among the three species and even between the two strains of mice (CF1 and what was termed "ABC," although this is not a bona fide strain of mice).

The authors speculated on the possible explanation for this dependence of retention on dosage, and, while attempting to uncover reasons, demonstrated

(a) Some of the very earliest animal work at the Met Lab was initiated by C. Ladd Prosser before either Dr. Finkel or Dr. Brues checked in at Chicago.

(b) These papers were scheduled for inclusion in volumes of the National Nuclear Energy Series (NNEs), which were never published. See Appendix C.

several important basic facts. First was the confirmation of much heavier concentration in the epiphyses of the long bones. Second was differences in deposition in different bones and in teeth, e.g., scapulae and spine were significantly higher than the average, while ulna-radius and teeth were significantly lower. Third, cortical bone metabolizes the radium more slowly than trabecular bone and thus acquires its burden more slowly and holds it more tenaciously. Since there is much more cortical bone than trabecular bone, it is possible that the higher dosage levels might "saturate" the trabecular bone pool and drive relatively more to the cortical bone pool, where it would remain more firmly fixed. Other possibilities could not be ruled out, however.

These were not long-term experiments compared to the durations involved in the work with humans or later postwar work with longer-lived animal species, yet a retention function was desired. Retention after the first ten days appeared to be essentially constant with time. But the range of points was large, and loss as a power function of time shown later in man by Norris, Speckman, and Gustafson (1955) could not be excluded. Indeed, their composite figure (figure 25) indicates the possible validity of the power function for the massed data.

The toxic effects of injected radium at these relatively high doses were gauged by the weight response and survival times. The prime features in the rat are given in the following excerpt from CH-3852 (1946): (a)

1. The earliest effect of radium on weight was seen in a rapid loss. The rate of loss was maximal on the first day and decreased on successive days thereafter.
2. At low injection levels ($0.1 \mu\text{C/g}$ and below), the loss of weight equilibrated almost completely within 30 days, and very little additional relative weight loss occurred until the animals went into their terminal decline.
3. At injection levels of $0.2 \mu\text{C/g}$ and above, the loss of weight was progressive. After the first 20 days, the rate of loss per day became nearly constant. The rate of weight loss increased with amount injected. This is shown quantitatively in table 3, which gives the slopes of the $\alpha(t)$ curves at the various injection levels. The mean rate of loss per day for all intraperitoneally injected groups is plotted against the retained amount of radium in fig. 3. The rate of weight loss is seen to increase in proportion to the amount of radium retained in the body.
4. The initial weight loss was roughly proportional to the amount of radium retained at low injection levels, but increased more slowly at higher injection levels. A measure of the initial loss for each injection level was obtained by determining the average value of Q over the period from 1 to 50 days after injection. This is plotted against retained amount for the 3 lowest injection levels where the initial weight loss was most nearly proportional to the retained radium (fig. 4). The weight loss of rats exposed to daily doses of x rays is also plotted in fig. 4 on the equivalent roentgen scale:

(Norris and Evans 1946)

Effects using survival time criteria are shown here in figure 1.2 for the rat and 1.3 for the mouse.

There appears not to have been a large serial sacrifice experiment done at this time. Thus, pathological observations are limited to those on autopsy at the end

(a) No attempt is made in quotations to translate to current terminology; thus $\mu\text{C} = \mu\text{Ci}$, etc. The numbers given for tables and figures refer to those in CH-3852 and are not reproduced here.

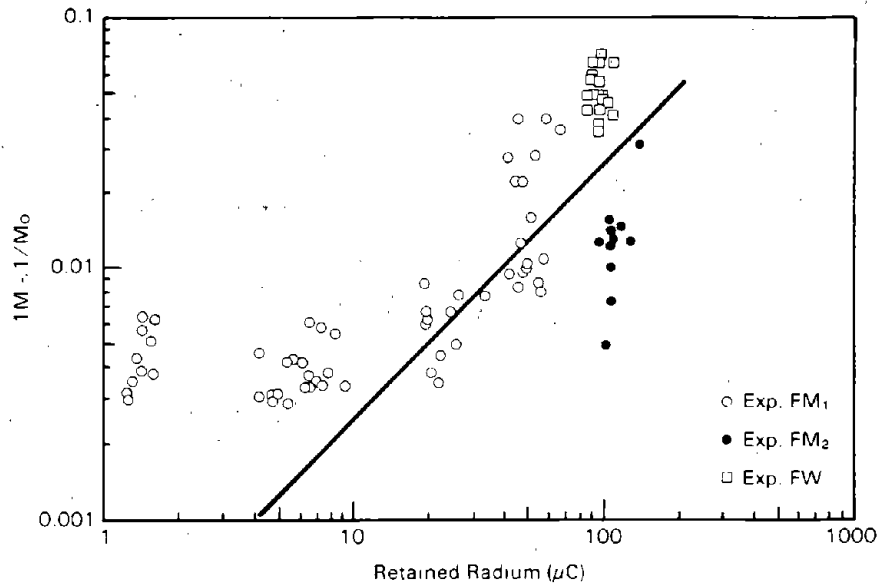


FIGURE 1.2. Influence of the radium content of rats on survival time. Survival is expressed as $(1/M - 1/M_0)$ where M represents the survival time of the treated rat and M_0 the survival time of the normal untreated control. (Redrawn from Norris and Evans 1946.)

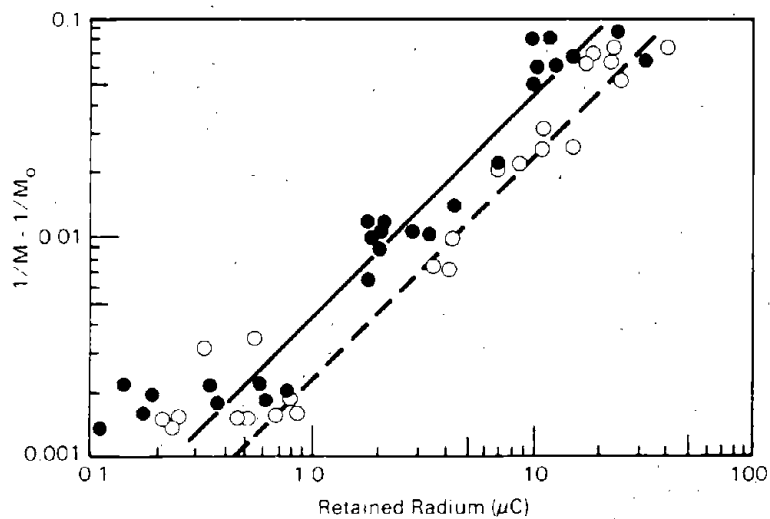


FIGURE 1.3. Influence of radium content on the survival time of CF1 female (●) and ABC male (○) mice. Survival is expressed as $(1/M - 1/M_0)$ where M represents the survival time of the treated mouse and M_0 the survival time of the normal untreated control. (Redrawn from Norris and Evans 1946.)

of the terminal phase for each animal and whatever observations could be made on the intact animal during the experiment.

Of special interest among the general pathological findings is calcification of certain soft tissues.^(a) This was most regularly seen in the aorta and resembled arteriosclerosis. It sometimes extended to the large arteries and to the heart. There were also foci of calcification in other soft tissues, usually associated with higher than normal concentrations of radium. This phenomenon was also seen in the Rochester experiments (see section V c). It seems not to occur with any of the other bone-seeking radioelements such as strontium and plutonium, or in fact with any other radioelement. For this reason, the authors considered a possible role of the radon produced from the deposited radium. Naturally no experiment with radium *without* radon could be done to check this postulate. Accompanying this deposition of calcium was a pronounced loss of elasticity of the affected blood vessels so that "the aorta and its branches resembled a system of rigid tubes or pipes" (Norris and Evans 1946).

There was also degeneration and necrosis of muscle fibers of the media of the aorta as seen microscopically.

While the calcification of the aorta occurred quite early in animals (rats) receiving high doses, calcification also occurred in other tissues when the dose was such that the animals lived in excess of one hundred days. There were calcareous lumps in the stomach and a chronic constrictive peritonitis.

The experiments with mice (ABC males and CF1 females) showed approximately the same gross toxicity and gross pathology. In the brown and black animals, there was decided graying of the hair. In the mice, a peculiar condition appeared in one or both eyes in which the eye, on gross examination, appeared to be filled with blood. There was evidence that this caused blindness in the affected eyes. The phenomenon was dose-dependent and occurred in about one-half of the animals living beyond thirty days. It did not appear in the rats.

Other pathology was similar to that seen after moderately high doses of external radiation. However, the calcification process seems to be unique to radium. It is somewhat surprising that this has remained only an observation in the years since this work was done. Both the Chicago and Rochester groups mused a bit on the possible mechanisms involved (and why only radium?), but there was no opportunity for mechanistic experiments then nor has there been clear-cut follow-up in more recent years. It seems likely that these animals had hypertension. Does such an effect extend in lesser degree to low doses and occur in humans as part of the delayed-effects syndrome? Relatively little mention is made of physiological findings in the radium patients and workers, just their anemia and effects in bone. It is not too late to look, however.

Osteogenic sarcoma was notably absent in these studies probably because the high doses terminated life before cancer could develop. One rat in twenty-one that received 15.4 μCi of ^{226}Ra (0.059 $\mu\text{Ci/g}$) developed an osteogenic sarcoma of the right femur, which was noted at 191 days after injection. There were metastases to the lungs. Similarly, one mouse in nineteen developed sarcoma. However, other symptoms of bone damage, such as fractures of the long bones and multiple fractures of the ribs, were common after 100 to 150 days in the rat. (The original report shows roentgenograms of these phenomena, including inability of the fractures to reunite firmly despite adequate callus formation.)

(a) This may be species-dependent.

The second part of this important unpublished series concerns hematological effects (Jacobson and Simmons 1946). Here it was possible to follow the development of effects with serial determinations at each dosage level. Rats, mice, and rabbits were used at dosages of radium chloride comparable to those in the experiment of Norris and Evans (1946), 0.005 to 0.94 $\mu\text{Ci/g}$ in rats, 0.000066 to 0.85 $\mu\text{Ci/g}$ in mice, and 0.0016 to 0.1 $\mu\text{Ci/g}$ in rabbits. Most of the injections were intraperitoneal. Since the results of the few intracardiac injections were very similar, the authors conclude that this difference in route of administration is not significant and report the results without separation by route.

No significant hematologic alterations occurred after an injected amount of 0.01 $\mu\text{Ci/g}$ or less of radium. Doubling the dose to 0.02 $\mu\text{Ci/g}$ produced both anemia and sustained leukopenia in the rats, but a further increase to 0.03 $\mu\text{Ci/g}$ was required to produce severe anemia in the ABC male mice and an initial moderate reduction in leukocytes. These changes were not seen even at this level in the CF1 female mice. The rabbit appeared more resistant still, requiring 0.1 $\mu\text{Ci/g}$ to produce even a moderate reduction in leukocytes and still more to produce anemia. Higher doses reduced reticulocytes and platelets. At the lower doses, the peripheral blood changes showed recovery until the terminal stages, but recovery was moderate or absent at the higher doses.

Follow-up on the possible validity of the species and strain differences seen does not seem to have been possible in this pioneering experiment.^(a)

There were morphological changes such as increase in red cell diameter and mean corpuscular hemoglobin, i.e., macrocytic anemia at doses in the 0.1- to 0.2- $\mu\text{Ci/g}$ range. These changes were similar to those seen after administration of either external x- or gamma radiation.

The other large experiment at Chicago involving ^{226}Ra was of much later origin. It began the now classic comparison of carcinogenic potency of several bone seekers relative to radium reported from Argonne National Laboratory in the postwar years. Since this is pertinent largely to comparative toxicity, discussion will be reserved for the chapters comparing radium with the fission products and the actinides. The fact that it was apparently begun under MED auspices should be recognized here, however.

A series of mice and rats given radium by intraperitoneal injection are listed in the appendix to Bloom's classic treatise on the histopathology of irradiation (Bloom 1948). The effects are taken up in conjunction with each major organ system and compared with beta-ray sources and x rays. The peculiar vascular changes are mentioned again along with the fact that the peculiar calcium-like deposits are highly radioactive. The Bloom book is a major compendium of the histopathology studies done by the Metallurgical Laboratory and should be consulted for both a broad overview and specifics for any radionuclides.

C. Experiments at Rochester with Radium-226

The work at the Rochester Project was done as part of a general investigation of the biological effects of alpha emitters. It was published in detail in the volume

(a) This experiment was paired with a comparable one using plutonium, and the report gives data on comparative effectiveness of plutonium and radium. This seems to be the first such comparison reported. It will be discussed in chapter 7.

edited by Robert Fink in the National Nuclear Energy Series (Fink 1950).^(a) As in many other instances, the work with ^{226}Ra was done primarily to establish "control" or bench-mark data for the effects of lesser-studied elements under the same experimental conditions in the same animal species. But they contributed also to our understanding of the effects of radium itself.

The volume (Fink 1950) contains a very useful historical background chapter by H. E. Silberstein (Silberstein 1950a), distribution and excretion studies with rats (Silberstein 1950b), and the results of two large experiments on the intravenous lethal dosage of polonium, plutonium, and radium in rats (Boyd et al. 1950 a,b).

The Rochester workers stuck fairly assiduously to the intravenous route of administration^(b) as "the only quantitative method of ascertaining how much radium is in the body as a whole and actually available for excretion or deposition in the tissues at any time" (Silberstein 1950b, p. 179). Besides acting as anchor points for the comparisons, the experiments were designed to help establish excretion rates for use in bioassay and the measurement of long-term retention.

Since the Rochester results are fully available in the open literature, they will be dealt with somewhat more briefly than the unpublished Chicago work. It is amply clear that the two groups worked quite independently, although they probably had interchange of results after the lifting of security measures at the end of the war. The doses, expressed as microcuries per kilogram, were in the same range as those already reported for the Chicago work. Each rat is reported individually like a clinical case report so that the reader can see what happened in each individual. Yet composite graphs are drawn to show general trends. This applies to daily excretion figures and the tissue contents in animals sacrificed serially from 1 day to 300 days. There are tables for tissue contents at 24 hours, 10 days, 50 days, 236 days, and 300 days.

The work on distribution and excretion in the rat can be summarized by pointing out the contrasts to man elucidated by the authors:

1. The rat excretes radium much more efficiently than does man.
2. The rat releases approximately equal quantities in urine and feces, whereas in the human only one-tenth of the total excretion is via the urine.
3. These apparent differences in excretion of radium do not explain fully the differences between rat and man.

There is no doubt from both these experiments and those at Chicago that radium leaves the bloodstream much more rapidly than kidney excretion alone can account for. There is no reason to believe this is not also true in man. The excretion kinetics as plotted in the composite curves show an extremely rapid decline in urinary excretion rate in the first twenty-four hours—over a factor of one hundred—and almost as rapid a decline in fecal excretion rate with time. The percentage of dose retained continues to fall off slowly over the period from a few days to three hundred days, somewhat in contrast to some earlier work that indicated almost no loss once the period of rapid excretion had ceased.

The Rochester workers made no point of retention being a power function of dose, as described by Norris and Evans (1946), nor do their data indicate it. The

(a) Although published postwar, all volumes in the NNES refer to work done during the MED days except for data collation, editing, etc.

(b) There were two experiments using oral administration.

range of doses is not quite as great as in the Chicago work, but sufficient to show an effect the size of that described by Norris and Evans. No explanation is apparent for this difference. Indeed, the contrast was not really known to exist until it was too late to check for explanations by further experiments.

Two rats were given radium orally in a single dose. The figures show considerable spread between the two animals, but confirm that radium is moderately well absorbed from the gut and that excretion continues at its higher level for somewhat longer than after intravenous administration. This phenomenon is seen with other elements and may be taken to reflect the fact that orally administered materials show less tendency to form radiocolloids in the blood and tissues.

The biomedical effects of injected radium chloride were investigated in two extensive experiments. Polonium and plutonium were involved also. These two experiments, reported by Boyd et al. in chapters 7 and 8 of the Fink volume (Fink 1950), included extensive general and some special pathology and hematological observations.

Weight response and survival time were used as quantitative measures of the lethal effects. A large staff of pathologists, hematologists, and a statistician took part in both experiments. In the first experiment, termed "pilot studies," from two to six rats per dosage level were involved, and dosages from 17 to 8,000 $\mu\text{Ci/kg}$ were given. The second experiment, termed "intravenous lethal dosage," involved approximately ninety rats receiving radium (out of five hundred in the total experiment) at doses from 240 to 6,430 $\mu\text{Ci/kg}$ of ^{226}Ra . There is extensive and well-organized documentation for all findings, including separate sections on the hematology. The principal results can be summarized as follows:

1. Despite the large difference in size between the two experiments, the results are roughly comparable. The second experiment, however, was large enough to establish statistical validity for LD_{50} calculations.
2. The LD_{50} for radium was 2,100 $\mu\text{Ci/kg}$ at twenty days, 735 $\mu\text{Ci/kg}$ at sixty days, and 320 $\mu\text{Ci/kg}$ at one hundred days. These indicate that radium is not a highly effective toxic agent in producing acute lethality. Many other elements are considerably more effective in producing acute lethal effects. (See later chapters.) A possible chemical effect may account for the sudden death during or close to injection of one or two animals receiving very high doses.
3. The pathological effects were in general comparable to those seen with acute doses in the range of 500 roentgens of whole-body x-irradiation. These effects included marked changes in lung, liver, and gastrointestinal tract; depletion with some regeneration of germinal elements of the testes; only a small depletion of functional elements in the ovaries; marked decrease of functional cells in all of the hematopoietic organs, with frank atrophy at higher doses.
4. The unique calcification of the large blood vessels described in the Chicago radium experiments was found in the Rochester work, along with calcification of the trachea.
5. Bone changes were largely seen as depletion of osteoblasts and osteoclasts in almost all animals and degeneration in the epiphyses of about a third of the animals receiving radium. Five sarcomas were seen in the pilot experiment—one an osteogenic sarcoma—but there were too few animals to establish this as being caused by the radium.

6. The hematological changes can be summarized by table 1.1, taken from the publication. These results were from the pilot experiment. The fall in leukocyte count appeared to be linear on a plot of log radium dosage against lowest leukocyte count in percent of original or control.
7. Retention was measured in some of the animals. When mean activity remaining is plotted on a logarithmic scale versus mean survival time on a linear scale, a two-phase relationship is seen: a rapid phase lasting up to about fifteen days, and a slower phase out to eighty days, both linear on the semilog plot. It is not possible to determine that this is really different from the power function relationship described in the Chicago work, partly because of the relatively short time-span involved.
8. Weight loss is continuous from injection to death, its rate being dependent on dosage.

TABLE 1.1. Summary of the Effect of Injection of Radium Chloride on the Peripheral Blood Count of Rats*

Blood Constituent	Remarks
Erythrocytes	300 microcuries per kilogram and above resulted in anemia provided animals survived
Hemoglobin	300 microcuries per kilogram and above resulted in anemia provided animals survived
% Reticulocytes	700 microcuries per kilogram and above, a fall; minimum level at 7 days followed by a rise; most rats from 17 to 1,000 microcuries per kilogram showed spiking elevation between 15 and 50 days
Platelets	Early slight suppression between 17 and 300 microcuries per kilogram; above 300 microcuries per kilogram, definite suppression
Leucocytes	Immediate fall from 17 through 175 and 700 microcuries per kilogram with terminal rise in leucocyte count; a greater fall in doses above this, reaching zero 24 days after injection of 4,000 microcuries per kilogram
Absolute neutrophils	Early fall after 17 microcuries per kilogram and above; up to 900 microcuries per kilogram initial fall followed by rise until animal's death; doses above showed less tendency toward terminal rises
Absolute lymphocytes	Definite fall after 51 microcuries per kilogram which increases with higher dosage; 22 days after injection of 4,000 microcuries per kilogram fall to almost zero.

*Comparison made with controls and initial counts.

Source: Reset from Boyd et al. 1950a, chapter 7, p. 285 in Fink 1950.

The information on relative toxicity of polonium, plutonium, and radium gathered in these experiments will be taken up in chapter 7.

One extremely useful feature of both the design of the Rochester experiments and the method of reporting the results is the closeness one feels to the original data. Unlike much reporting in more recent years, forced upon us by the pressures of publication space and cost, it is possible to follow either individual animals or individual entities of relatively small scope in each experiment. Thus, the work contributes a feeling of security about tracing each conclusion,

each statement of fact, to the original data or closely related summaries. The monograph also gives very complete details on methodology for handling the injection solutions, animal care, assay of tissue and excreta and so forth.

D. Radium Research at Massachusetts Institute of Technology-Harvard-Massachusetts General Hospital During World War II

The Massachusetts Institute of Technology-Massachusetts General Hospital (MIT-MGH) program was already well established with financial support from philanthropic foundations and other sources when the Manhattan Engineer District was organized. It did not become officially a part of the MED effort. In fact, its personnel were involved in a variety of war research activities along other lines, and the radium work was not front and center to the degree it had been. Nevertheless, the task of measuring radium body burdens in patients, dial painters, and other workers continued, in part, by taking the Sundays not devoted to war work. Some things that could not be done at the time were put aside for postwar studies. Mary Margaret Shanahan, Dr. Evans's invaluable administrative and research assistant, kept doggedly at the task of compiling the rosters of individuals who did, or might, have significant body burdens, and of following up those who had been in for measurement. A group of dial painters from the Waterbury Clock Company, Waterbury, Connecticut, was added to the file, among others, for checkup and follow-up. Since the results of these studies fit easily with reports of later postwar years, details will be reserved for the section describing those years.

Between 1936 and 1941, the MIT group engaged in one of its few forays into work with animals. There were four series of experiments involving Wistar rats that were fed radium from medicine droppers or given intradermal injections (one series). Since the results were not reported until 1944, in two papers, they fall into the time-span of this section. The first paper, by Evans, Harris, and Bunker (1944), considered both metabolism and effects. The second paper, by Dunlap et al. (1944), concerned largely effects, especially the development of transplantable osteogenic sarcomas by feeding radium. The doses were moderately large in the aggregate (50 to 100 μ g fed) and were given as daily or every-other-day feedings, for a period that varied from ten to twenty days. Actual doses were calculated by first measuring the gamma-ray activity of the unopened ampule and subtracting from it the activity remaining in droppers, bottles, glove washings, and empty ampules. The sources of the radium were different and contained varying ratios of barium to radium, but the authors evidently found no difference in results attributable to this factor. Radium contents of tissues and residuum were measured using both the radon and the gamma-ray detection methods. As is characteristic of most work with radium salts handled in glass, there was a fairly large spread in actual dosages compared to the intended dosage. However, the authors report data for each animal individually so that this factor does not complicate the reporting.

The results can be summarized as follows:

1. The metabolism results, like those already discussed, showed very rapid initial excretion. Average retention at the time of death was about 2.2% of the amount fed. Excretion rate after the initial rapid phase ranged from 0.14% to 0.6% of the body content per day.
2. The rat exhales a much higher fraction of the radon produced from radium decay than does man. Radon exhalation averaged 85% of the body radium

- exhibited during life. The remaining 15% showed as gamma-ray emission. There was less exhaled as radon after intradermal injection (60% to 75%).
- 3. The skeleton contained most of the radium. The other organs contained less than 1% as much radium per gram.
- 4. Of the soft tissues, lung generally had the highest and heart the lowest concentrations.
- 5. Osteogenic sarcoma was found in each set of experiments and was transplantable.^(a) The lesions reproduced with fair fidelity the osteogenic sarcomas seen in the human radium cases, as did other aspects of the pathology.
- 6. An outstanding difference between rat and man was the finding of hypoplastic bone marrow in the rats. In contrast, the dial painters had a hyperplastic, regenerative marrow.
- 7. Perhaps the most critical difference was in the apparent sensitivities of rat and man to radium. The rat requires, according to these experiments, from 150 to 200 times as much radium in the skeleton to produce chronic symptoms comparable to those seen in man. On the basis of skeletal ratio of radium to calcium, the factor is at least 250. These facts so impressed Robley Evans that he vowed never to indulge in another experiment with animals intended to provide information needed for direct application to man. And to nail down the contention that the rat is unsuitable for any quantitative applications to man, the authors appended a table showing ratios between rat and man for the maintenance dose of certain vitamins and essential minerals, and for the toxic dose of eight metals. In every case, the rat was found to be less sensitive by ratios of from 1.9 to 152.0. Dr. Evans has participated throughout his career in joint endeavors among physicists, biologists, physicians, and others, and continues to do so. He has acted as advisor to later important animal experiments. But in terms of his personal research, he seems to have maintained his resolve to eschew animal experiments, maintaining with Pope that "The proper study of man is man" (Evans 1978a,b).

E. Other Studies

Obviously, there were other investigations of radium in man and animals during these years, but they fall in general outside of the scope of this work. Mention should be made of a few, however.

- 1. Dr. Frank Hoecker with the U.S. Public Health Service during part of the period of our interest, and later at the University of Kansas, published in the *Journal of Industrial Hygiene and Toxicology* on the use of the Rn/CO_2 ratio in breath as an index of excessive radium absorption, and on the coefficient of elimination of radium (Hoecker 1944a,b). Hoecker continued in the field for many years as sort of an independent, not directly associated with any of the major groups.
- 2. The MED supported work on carcinogenesis in the laboratory of Egon Lorenz at the National Cancer Institute. Most of this concerned external

(a) It should be noted that a Dr. Austin M. Brues is acknowledged as having explanted and grown fragments of two tumors in tissue culture. This was during his early years with the Harvard group and before he became involved with the MED at the Met Lab and later the AEC, as Director of the Biology Division of Argonne National Laboratory.

radiation and radon, but there was some work on radium metabolism in the mouse. This was issued as a declassified report from the Argonne National Laboratory, which was the contractor for Lorenz's project at the time of publication. (See Weikel and Lorenz 1947.)

3. A series of papers appeared in translations of USSR work indicating increased yields of crop plants in the presence of radium and other radioactive elements. Shades of the polemic of the previous decade in human medicine! They also reported the uptake and metabolism of various elements by plants. Since these papers were seen only as abstracts, no judgment can be made on the validity of the particular conclusions drawn. But the idea of stimulation of plant growth by radium was popular in the United States throughout the 1920s and 1930s (see Badash 1979). Indeed, the apparent stimulation of many life processes at low levels of assault by injurious agents may be a ubiquitous phenomenon. Whether the "stimulation" is for the ultimate good of the organism involved or not is problematical. It may still be of benefit to a party interested in crop yields, for example, but is likely to be injurious in the long run to the organism "stimulated" (see Dubkov 1940, 1941).

VI. Postwar Radium Research

A. General Comments

The uncertainty that clouded the future of many of the wartime research efforts when World War II drew to a close naturally included the plans for continuation, expansion, or contraction of research with radium. But two important differences from the general atmosphere greatly reduced its impact. First, the scientists involved were, in general, doing something closely akin to their permanent interests. There was not the mass exodus to return to environments and fields of research interrupted by the call to war work.

The MIT-MGH group was ready and more than willing to bring the radium studies from the back to the front burner. The Chicago group, although decimated in other areas, had the good fortune to have most of those concerned with the radium studies remain happily on the job. At Rochester, many of those who were closest to the radium work migrated to California. But those with long-held interests, e.g., William F. Bale, remained, and new, postwar staff continued the general program with internal emitters, including ^{226}Ra .

The second difference was financial support. The newly organized Office of Naval Research (ONR) stepped into the gap between the termination of support from the wartime agencies and the beginning of direct support from the U.S. Atomic Energy Commission (AEC) with most timely and far-sighted financial help. This included the work on radium at MIT.

The decades from 1947 until the late 1970s, the theoretical cutoff point for this chapter, turned out to be the best era yet for research with radium. The human cases named for follow-up went from a few hundred to at least twenty-five hundred (Brues 1976) individual files. Indeed, the total register may now have reached five thousand names (Rowland, Stehney, and Lucas 1977) if all of those suspected of having been exposed to radium, and potentially traceable, are included. The number for whom measurements of radium contents exist approximates sixteen hundred. Vigorous efforts are continuing to locate and

study as many as possible of those remaining. The information gathered has been standardized and computerized. Sufficient data are now available to describe retention functions with considerable confidence.

Along with the studies on man, radium was introduced into the long-term animal experiments started after the war. This has added the virtues of controlled experimentation where the doses are well known. Also, many of the questions of relating data gathered from animal experiments to the situation in man can be attacked with significant data on both sides of the equation.

In the postwar atmosphere, much more attention could be paid to basic mechanisms. It would not be an exaggeration to say that a large portion of the new knowledge about the dynamics of minerals in bone and the probable mechanisms of effects is tied to the work with radium and other bone-seeking radionuclides.

Also, new populations were discovered. These included a set of dial painters in Ottawa and La Salle-Peru, Illinois; and in Pittsburgh, Pennsylvania; and an entirely different set of exposed people in Germany. The latter involved the shorter-half-life (3.6 days) isotope of radium, ^{224}Ra , the study of which, while far from complete, has already added materially to the broad picture of radium toxicology.

These developments will be taken up in whatever detail is relevant to the purposes at hand in the sections below, starting first with the oldest and longest continuous study, the MIT-MGH work.

B. Postwar Radium Research at the Massachusetts Institute of Technology

Dr. Robley D. Evans had the pleasure one Saturday morning around V-J day of a visit from a Dr. Robert Conrad of the newly formed ONR. Conrad stated, "We have selected some laboratories over the country which we regard as national assets. The Admiral^(a) says yours is one of them. How much money do you want?" Evans, always the pragmatist, asked what they were supposed to do. After all, the military had been requesting specific jobs ever since 1941. The response implied that there were no strings. Just keep on doing the radium work they had been doing.

Thus began one facet of a saga too little recognized in the history of scientific research in the immediate postwar years. While the struggle over civilian versus military control of atomic energy raged and was finally resolved by organization of the AEC, the ONR stepped in to keep important groups together and to keep continuity in important projects. This was done first by direct use of Navy funds and later by use of funds appropriated for the AEC but distributed and administered by ONR while the AEC was getting organized.

As soon as the AEC was organized and had a director for the Division of Biology and Medicine—Dr. Shields Warren from Harvard-New England Deaconess Hospital—Evans was encouraged to bring the radium work, especially the crucial follow-up of the dial painters, chemists, and other radium workers and patients with the iatrogenic body burdens, into full bloom. From that point forward, the MIT-MGH work, which had depended largely on

(a) "The Admiral" was probably Rear Adm. H. J. Bowen, former head of the Navy's Special Devices Center who had much to do with the launching of the Office of Naval Research.

nongovernmental sources of support, was an official activity of the United States government through contracts. It still is, although differently organized.

Space does not permit a detailed review of what was done, nor is it needed since the annual reports and numerous summaries at symposia provide easy and in-depth documentation. Some of the highlights will appear in this section.

1. Growth of the Populations

The numerical growth of the total population at all laboratories has already been summarized. The MIT group, up to the time of consolidation of their studies with those at Argonne National Laboratory, had studied about 800 individuals, some 600 or so living, about 60 by autopsies of exhumation cases, and 120 unexposed matched living controls (Evans, Keane, and Shanahan 1972). The process of follow-up on the dial painters from the Waterbury Clock Company and New England Watch Company, begun during the war, was expanded. The New Jersey dial painters, studied for a while in an independent project, were eventually folded in to a considerable extent. A new population of dial painters was added from the Standard Chemical Company in Pittsburgh.^(a) The circumstances of this find are described in the following excerpt from the May 1961 Annual Progress Report of the MIT Laboratory (MIT 1961):

For the first time there have been a number of patients from the Pittsburgh area. When the Flannery Building was being renovated for a new tenant, it was found that a very extensive decontamination job had to be done to eliminate the radioactive material which remained from the period when the Standard Chemical Company occupied the 4th and 5th floors. This contamination received a great deal of publicity in the Pittsburgh area and this in turn prompted former workers of the Standard Chemical Company to get in touch with the State Department of Health. Every attempt was made to reassure these people that there was very little likelihood of their having suffered any damage. Workers from the State Department of Health interviewed a large number of these people and collected breath samples in flasks from a number of them. Former dial painters and chemists were encouraged to be tested for residual radioactivity either at MIT or at Argonne National Laboratory. Nineteen individuals came to MIT where a complete battery of tests, both medical and physical, were carried out (see Tables 5 and 6).
(MIT 1961, p. 13)

Each annual progress report gives details not only of the source of the individuals studied in the several populations, but protocols of the data obtained from those studied during that particular year. The population was broadened to include a large variety of sources, even some cases bearing a body burden from thorium-series isotopes gained by the administration of Thorotrast (see chapter 4).

2. What Is a Suitable Population?

The reports from the MIT group emphasize the possibilities of bias brought into the populations studied. (These problems were, of course, general to the field and were recognized by most workers to a varying degree and with varying ideas for solution.) The early population was made up almost entirely of individuals who either sought aid because they had symptoms or were referred by physicians who suspected their problems might have been caused by deposited

(a) Some of these were also studied at the Argonne National Laboratory in the late 1950s and the 1960s.

radium. These are frequently described as "walk-ins." Their counterparts without problems would be unlikely to enter the study. The "walk-ins" were designated by the MIT workers as in general "*epidemiologically unsuitable*" for purposes of establishing dose-response relationships.

Throughout the postwar decades at MIT, much of the effort was to bring in all possible exposed persons for measurement and thus broaden the base of epidemiologically suitable subjects. This follow-up included bringing numerous persons to MIT for measurement or securing breath samples for radon measurement plus whatever medical information could be obtained in situ from those who could not or would not come to be measured. It also included much work in arranging for exhumations as well as the estimation of body burden through measurement of samples of bone obtained from deceased individuals at autopsy.

These efforts have undoubtedly reduced the bias in the effects data. Evans has been very careful to use only what he regards as the epidemiologically suitable cases for any quantitative determination of dose-effect relationships (Evans, Keane, and Shanahan 1972). There are those who feel that any overrepresentation in the registry of cases with symptoms may be balanced by underrepresentation of early cases with high burdens who died before the studies began, as well as those with low burdens who died from other causes before they could be included in the registry. Nevertheless, from the standpoint of pure epidemiology, the study is still open-ended since a surprisingly large number in the registry are alive today. In fact, many are expected to live well into the twenty-first century. The books cannot be closed nor the study curtailed until after this final stage. This is true even though satisfactory statistical validity was attained by the mid-1960s.

3. Expression of Dose

In the earlier MIT measurements, the radium burden was expressed in microcuries, or micrograms. As knowledge expanded concerning the biological effects from x or gamma or other external radiation sources, it was tempting to translate microcuries into absorbed dose in rad for comparative purposes. The MIT studies gradually shifted from simple microcuries to "pure radium equivalent" (see next section) and to "cumulative rad." As Evans, Keane, and Shanahan (1972) explained, many of the biologically relevant dosage parameters such as measured residual body burden, extrapolated initial burden, and maximum dose rate do not convey information concerning the protraction of the radiation insult. A unit involving some integral of rate and duration of the irradiation was desired. What was utilized, for convenience only and not to be interpreted as representing the dose to individual target tissues, was the gravimetric average skeletal absorbed dose expressed as cumulative rad or "CR." The nuances of this choice are detailed in Evans's Sylvanus Thompson Lecture (Evans 1966). Most recent summaries from the MIT group utilize this mode of expressing dose from radium. It can be regarded as a forerunner of committed dose equivalent and related entities of more recent origin.

4. The Role of Mesothorium—The MsTh/Ra Ratio

The dial-paint mixture used in the early days was not of constant composition either among different plants or at different times in a given plant. The chief variable was the presence or absence and amount of ^{228}Ra (classically called

"mesothorium," MsTh). It has a much shorter half-life than ^{226}Ra , about 5.7 yr^(a) versus 1,600 yr for ^{226}Ra . It will be remembered that the early paints had so much MsTh that Martland described the early cases as "mesothorium poisoning." Because of the shorter half-life, the MsTh delivers its radiation dose, and that from its daughters, much sooner than ^{226}Ra on an equal microcurie basis. Thus, depending upon the amount of MsTh in the compound, the actual radiation dose may be many times greater at early times than that inferred from the residual ^{226}Ra measured many years after exposure.^(b)

Proper estimation of radiation dose to the dial painters requires good determination of the presence or absence of mesothorium and its decay products and the ratio of MsTh to ^{226}Ra at the time of measurement, a difficult and uncertain task. The MIT group did their best, including diligent attempts to get samples of the paint used, which would provide activity levels in the range of the instrumentation available.^(c) If that failed, in-vivo measurements of thoron exhalation were made. The very short half-life of thoron (54 sec) made that a difficult task because:

not much was left for exhalation;

transfer from the site of release to the lungs is far from complete and is quite variable;

the gas decays so quickly after collection that the actual measurements were frequently of the thorium B and C decay products, which plated out electrostatically on the surfaces of the collection devices.

The annual reports of the 1950s give us a clear picture of the frustrations of such measurements, even in a laboratory devoted primarily to applied physics.

The advent of the sodium iodide crystal counter and, later, installation of a whole-body counting facility at MIT (which they called "controlled background facility" or "CBF") changed all of that (MIT 1959). The 2.62-MeV gamma ray from ThC, one of the daughter products of mesothorium, could be measured with relative ease so long as appreciable quantities of MsTh had been present originally.

On the basis of these and earlier measurements, it could be concluded that, in about half of the MIT cases, from 50% to 90% of the total alpha-radiation dose came from the MsTh chain. In the rest, it was much smaller.

- (a) The half-life was thought to be about 6.7 yr until C.W. Mays (Utah) recognized an ambiguity in the decay data. The more reliable value was pointed out in the 1960 annual report from MIT (MIT 1961, p. 1415).
- (b) Radiothorium (RaTh), the second product in the MsTh decay series and an alpha emitter, is actually of much more importance than MsTh itself, which is a beta-particle emitter. A detailed exposition of these relationships is given by Aub et al. (1952).
- (c) The variable use of mesothorium in self-luminous compounds by one company, the United States Radium Corporation, is shown vividly in table 1 of Aub et al. 1952. In the period 1917 to 1923, the MsTh/Ra ratio, expressed after three years of aging, was 0.92; in 1926 it was 0.32; in 1927 it was 0.23. Some confusion has been introduced into the literature by attempts to lump together luminizers from one company as "high mesothorium" and others as "low mesothorium." This requires great care in ascertaining the time frame. Also the nostrum "Radithor" showed great variability with time. Thus, the safest path is to know the individual MsTh/Ra ratio. Only the Ottawa, Illinois luminizers and the radium patients who received intravenous injections can be reliably thought to have received pure radium.

A striking illustration of the relative contribution that mesothorium can make to the total alpha dose is seen in figure 1.4, taken from Aub et al. (1952).

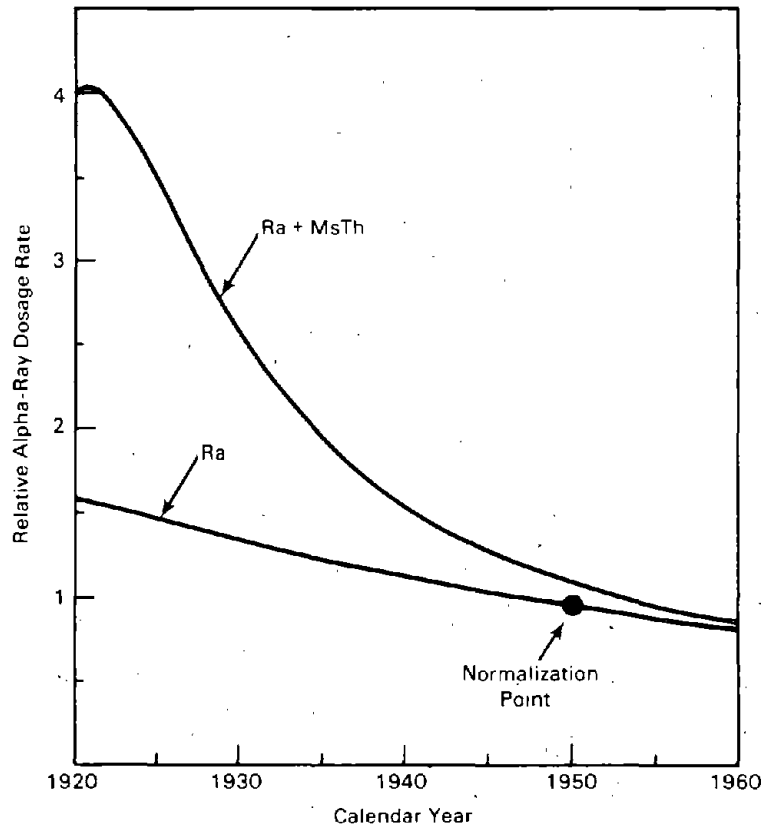


FIGURE 1.4. Illustration of the importance of the dose from mesothorium especially in the early years. The lower curve shows the alpha-ray tissue dose from ^{226}Ra , assuming it was ingested in 1920. The excretion rate has a half-period of forty-five years, and the ^{226}Ra dose is taken as unity in 1950. The upper curve shows the total alpha-ray dose from a mixture of MsTh and radium in a paint of average composition in the period 1917 to 1923. (Redrawn from Aub et al. 1952, p. 323. Reprinted with permission of The Williams & Wilkins Co., Baltimore, copyright 1952.)

5. The Pure Radium Equivalent

Even before the advances in instrumentation made measurement of mesothorium an easier task, the need was felt for a single unit that could express the radiation delivered to the skeleton in cases with quite different fractions of the dose from MsTh versus ^{226}Ra . The MIT group developed an expression for this known as the Pure Radium Equivalent or PRE, defined as:

$$\text{PRE} = \left[1 + \left(\frac{\text{present MsTh/Ra ratio}}{\text{ratio}} \right) \times \left(\frac{\text{MsTh decay since first exposure}}{\text{decay since first exposure}} \right) \times \left(\frac{\text{ratio in rad/}\mu\text{Ci}}{\text{MsTh/Ra}} \right) \right] \times \mu\text{Ci-}^{226}\text{Ra}.$$

If it is assumed that the present MsTh/Ra ratio can be measured, and the time of initial exposure is determinable, the rest follows by using a physical half-life of 5.7 yr for MsTh and adjusting the ratio of rad/ μ Ci for MsTh compared to radium according to the time since deposition, the relative energies imparted by the thorium and radium decay chains, and the respective fractions lost in the gaseous daughters (Evans 1967). In typical cases, the PRE may be boosted to as much as ten times the dose associated with a comparable amount of ^{226}Ra alone. Let it be emphasized, however, that the end result is still in rad. As we shall see in a subsequent section, there is reason to believe that rad from ^{228}Ra are more effective by a factor of two to three than rad from ^{226}Ra .

It must have been during this period that Dr. Louis Hempelmann nearly froze. Hempelmann, a physician-radiologist now at the University of Rochester Medical School, was in the early 1950s part of the medical team at Harvard-Massachusetts General Hospital, which did the clinical work-ups on the MIT patients. Evans and Hempelmann had been musing on the many unexplained differences among the dial painters and Radithor drinkers compared to the radium patients and chemists. The possible contributions of MsTh were, of course, much on their minds, but they had not been able to be quantitative. Indeed the data were very unsatisfactory. By the time of this incident, Hempelmann had moved to Rochester but was still much involved with the radium work. He was at home one cold day enjoying a hot postexercise shower (Hempelmann is an avid squash player) when he received a message that Dr. Evans wanted him on the telephone. Wrapping a towel about his middle, he proceeded to the phone to find Evans ecstatic over the way the now measurable mesothorium content explained many of the differences. The enthusiasm lasted for one and a half hours and might have gone on longer except for the noise of Hempelmann's teeth chattering!

6. The Biological Effects

A landmark paper describing the effects of deposited radium in man is the one already cited in another connection by Aub et al. (1952). While it takes up only thirty patients, a small fraction of the total by the late 1960s, the analysis is so thorough and detailed that subsequent work needed only to relate to one or another of the examples given in this paper. There is a complete clinical description of each case along with a review of the pertinent biological and physical properties of radium and mesothorium.

The sophistication of the biomedical studies of the radium cases had grown apace with the improved physical measurements. By the 1960s, a battery of fifty-six biomedical parameters for measurement was developed (Maletskos et al. 1964; Evans 1967). The easiest among these was, of course, the development of frank malignancies. But skeletal changes of more subtle nature were important too. To quantify these, a system was worked out by Dr. Gary in collaboration with Drs. Robert J. Hasterlik and Asher J. Finkel of the Argonne group based upon the examination of roentgenograms. A sample of the scoring sheet is given by Evans (1967) and in other reports from MIT. The scoring system was tested repeatedly by all concerned until they were satisfied that there were few, if any, differences in interpretation of the radiographs (Hasterlik 1980). This scoring system, called the x-ray score, became one of the most satisfactory measures of overall effects of the radium and daughter products on bone. Many of the MIT results are presented as x-ray score versus PRE.

After some further use, it was deemed desirable to show results in two ways, with or without the sarcoma incidence included. (Sarcomas rated a five, the highest score in the system, and tended to overload the picture for scoring other changes.) The score with sarcomas included became known as the "classical x-ray score," that without the sarcomas as the "reduced-x-ray score." In the later reports, one or the other of these was plotted against cumulative rad (CR) in presenting the results.

A plot of classical x-ray score versus dose in cumulative rad for the MIT cases studied through 1969 is reproduced as figure 1.5. Tumor incidence in the same MIT cases is shown in figure 1.6.

In both instances, there appears to be no effect below somewhere around 500 CR on the basis of the classical x-ray score or below about 1,000 CR on the basis of cumulative tumor incidence. It appears that the classical x-ray score continues to rise with dose, but the tumor incidence levels off at about 30%, except for the very highest CR doses, where it may be higher but not outside the range of mean occurrence.

This relation has held up through many testings and much manipulation of and additions to the data. Since tumor incidence times increase with decreasing doses (see figure 3 of Evans, Keane, and Shanahan 1972), it can be argued that the latent period for tumor formation becomes longer than the life span of the individual at about 1,000 CR. The relationship was taken by the MIT-MGH group as indicating there is a domain at low doses that can be designated as a *practical threshold*. The failure of tumor incidence to increase beyond about 30% can be interpreted as saying that only about 30% of human beings can develop bone sarcoma no matter what the dose from radium.

A considerable polemic has grown up around these relationships, and dose-response curves have been derived from other sources and with other elements, as we will see. For our present purposes, it is enough to present these relationships as summary findings from the MIT work derived from a set of internally consistent and exhaustively analyzed results.

It will be noted in figure 1.5 that the tumors include carcinomas of the sinus or mastoid in addition to bone sarcomas. The carcinomas are thought by some to be due to radon released from radium decay that can enter these air chambers and bombard the mucous membrane lining as well as deposit decay products on the surfaces. This could, of course, be an effect associated uniquely with radium deposits and not mesothorium or other bone seekers that do not release appreciable quantities of alpha-active gas. However, mastoid and paranasal air cells have epithelium closely applied to bone that may be bombarded directly by alpha particles emanating from bone surfaces. Thus, the effect cannot be tied solely to radon emanation. In recent years, cancer of these areas has been found in many other inhalation exposure situations. The story is still unfolding.

As Stannard stated (1973), the 1972 paper by Evans and colleagues constitutes a sort of valedictory on the forty-plus years of work of the MIT Radioactivity Center. It reflects not only the careful analysis of accumulated work but bespeaks the wisdom of the Office of Naval Research and later the Division of Biology and Medicine of AEC in keeping the Laboratory and the group intact and prospering.

After a discussion of radium studies at Argonne, we shall examine the work of the Center for Human Radiobiology, which was formed by a consolidation of the MIT and Argonne cases toward the end of the period we have been examining.

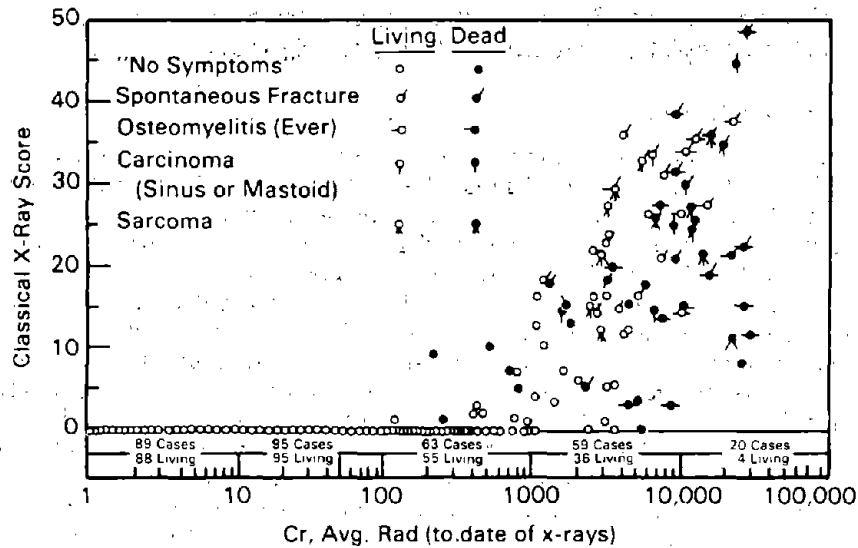


FIGURE 1.5. Correlation between the classical x-ray score and average cumulative rad (CR) for 326 cases in the MIT-MGH study. (Redrawn from Evans, Keane, and Shanahan 1972, p. 439. Reprinted with permission of J. W. Press, Salt Lake City, copyright 1972.)

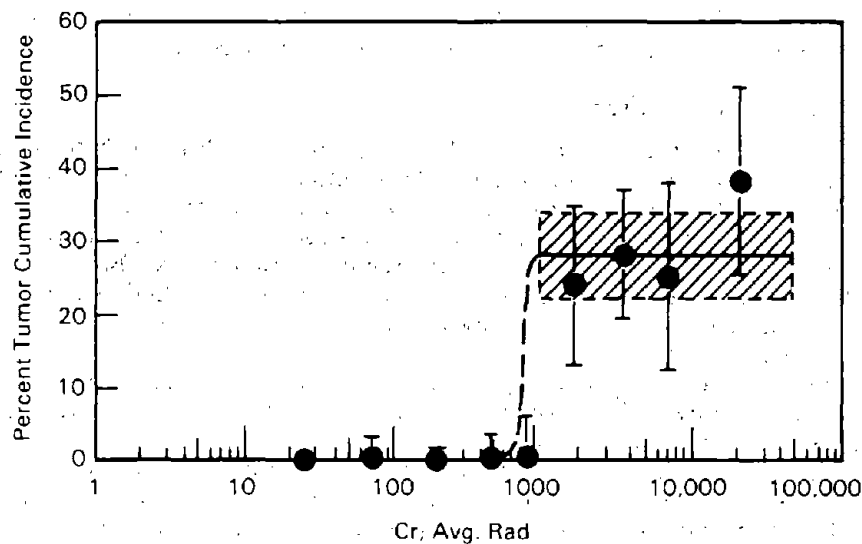


FIGURE 1.6. Observed tumor cumulative incidence or occurrence in the "Epidemiologically Suitable" cases and low-exposure cases (zero incidence of malignancies) in the MIT-MGH cases measured prior to May 1969. (Redrawn from Evans, Keane, and Shanahan 1972, p. 447. Reprinted with permission of J. W. Press, Salt Lake City, copyright 1972.)

C. Postwar Radium Research at Chicago (Argonne National Laboratory/Argonne Cancer Research Hospital)

1. General Comments

At the end of World War II, the Metallurgical Project gradually dissolved along with the Manhattan Engineer District. The Chicago portion became the Argonne National Laboratory (ANL) with new buildings and equipment built outside of Chicago near Lemont, Illinois, and hard by the site of the old Argonne reactor. Biology and Health Physics Divisions were organized, the animal facilities were greatly improved, and a major interrelationship with the University of Chicago Medical School developed. A bit later, potential for clinical input was increased by the organization of the Argonne Cancer Research Hospital (ACRH). There was a loose connection between this new organization and the Argonne National Laboratory, which was most fully expressed in the radium studies.

The Division of Biological and Medical Research of ANL was directed by Dr. Austin M. Brues, whose contact with radium work we have already noted. John Rose, a well-known radiological physicist headed the Health Physics (soon renamed Radiological Physics) Division, and he worked in close association with Leo Marinelli, who was associate director for research. Both of these men, especially Marinelli, and their associates had strong interests in internal emitter toxicology.

The Laboratory became and has been a leader in all fields of postwar atomic energy research. The biomedical program, although somewhat modified in general emphasis, maintained the work with radium already under way and added major new work. Because of the association with the ACRH and the presence of physicians such as Drs. A. Finkel and R. Hasterlik in the program, much more work on human patients and workers could be added.

2. Retention of Radium

In section V, we reviewed early work done primarily by William P. Norris and associates on the metabolism, i.e., transfer functions, of ^{226}Ra . Most of the studies reported then were from animal populations. After the war, these were extended into long-term studies on man, primarily, but not exclusively, the patients at the Elgin State Hospital where Schlundt had measured body contents in the 1930s. Norris's work was actually begun during the MED days but had to extend into the postwar years to allow for evaluation of long-term kinetics of retention and excretion.

Earlier in-house reports and general conclusions were well summarized in two papers published by Norris, Speckman, and Gustafson in 1955 and by Norris, Tyler, and Brues in 1958.

The results confirmed much of the earlier work on the metabolism of radium and extended its range and sophistication. Perhaps of most import for future work was the mounting evidence that the power function relationship seen in the animal work was even more clearly descriptive of retention of ^{226}Ra in man. It took a special effort to make this conclusion stick. Most radioisotopes leave the body by first-order kinetics (i.e., as an exponential function of time). The power function had no obvious basis in physiology and has its difficulties of application to very short times. But the data kept giving straight lines when plotted as log retention against log time. The power function was gradually accepted as probably the best description and was used for calculating radium

burdens extrapolated to times prior to or after the time of a measurement. It became known as the "Norris function."

After a single intravenous injection, the relation took the form $R(t) = a t^b$ where R is retention, t is time after administration and is ≥ 1 , a is a constant providing the intercept at unit time, and b is the slope of the straight line on the double-log plot, which has a negative value. For some years, the values given by Norris, $a = 0.54$, $b = -0.52$, were utilized. Later C. E. Miller and A. J. Finkel (1966) re-examined the data and made additional radium body-burden measurements on the same State Hospital patients. They arrived at somewhat different constants based on the arithmetic mean of the slopes and a geometric mean of the individual intercepts. These were $a = 0.30$, $b = -0.44$. The range was from $a = 0.18$, $b = -0.22$, to $a = 0.89$, $b = -0.63$. The new average values were used when individual data were not available, which was frequently.

The reports of Miller and Finkel carry an importance beyond the quantitative change in constants. The subtitle of their published paper (1968) is "The Power Function Re-Evaluated." Because of continuing skepticism over the validity of the power function, the work was as much to see if it still held as to get improved values for the parameters. It has held.^(a) The MIT group began using the power function after finding it worked for their data, although with somewhat different constants ($a = 0.54$, $b = -0.52$ [Evans, Keane, and Shanahan 1972]). The beagle dogs at Utah, to be described later, fell in line too. In fact, other alkaline earth elements, such as calcium as represented by ^{45}Ca and strontium as represented by ^{90}Sr , seemed to be retained by functions that were also power functions of time in both man and dog (Rowland 1959). This concept extended even to barium. It may thus be a characteristic of the alkaline earth group of elements or of bone seekers in general.

Obviously for multiple doses, either intravenous or oral, the simple relation needed modification. This was done by the Argonne group, and curves for radium retention after oral ingestion for various periods were worked out on the basis of the power function, with the results shown in figure 1.7, taken from Finkel, Miller, and Hasterlik (1969b).

The picture after a series of fifteen weekly intravenous injections is as one would expect: a series of spikes followed by double-logarithmic decay after cessation (see figure 2 of Finkel, Miller, and Hasterlik 1969b).

All of these metabolic studies were, of course, greatly facilitated by the development of a "whole-body counter" facility at Argonne. This was one of the pioneering efforts for which credit goes largely to Leo Marinelli and Charles E. Miller (see chapter 17).

3: The Argonne Radium Studies

"The Argonne Radium Studies" could of course apply to all of the work with radium done at ANL. But it is reserved for a discrete facet of the work involving man. It encompassed compilation of the clinical effects in a diverse group of the Elgin State Hospital radium patients, the new group of former dial painters, individuals throughout the Chicago area who had received radium as a therapeutic measure from their physicians, and some radium chemists and other

(a) Of course a series of exponentials if close enough in slope can merge into a linear relation on a double-log grid; and the data could be described in this way too. Hence the confirmation is not absolute.

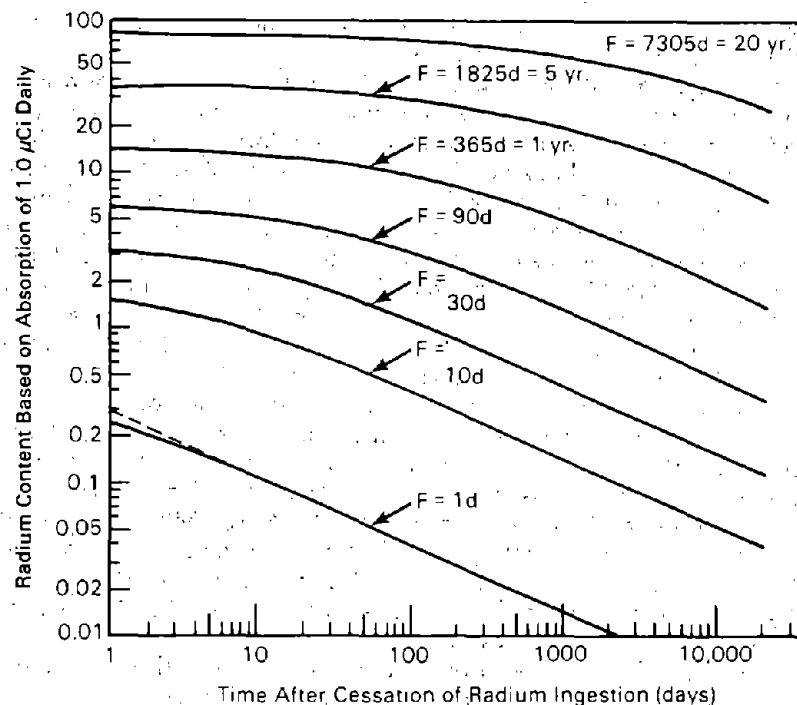


FIGURE 1.7. Log-log plot of radium retention after cessation of oral ingestion. Periods of ingestion are given as factor "F" on the curves. Assumptions were: daily absorption of 1 μCi . Power function parameters: $a = 0.30$, $b = -0.44$. (Redrawn from Finkel, Miller, and Hasterlik 1969b, p. 199. Reprinted with permission of University of Utah Press, Salt Lake City, copyright 1969.)

workers. The clinical evaluation was coupled with measures of the body burden and extrapolation to the presumed original or maximum body burden.

The story has been summarized very well in several reviews (Looney et al. 1955; Finkel, Miller, and Hasterlik 1959; Hasterlik, Miller, and Finkel 1969; and Finkel, Miller, and Hasterlik 1969a,b). One of the most complete but least portable of the summaries is found in special ANL reports devoted to a review of all patients to the date of writing (Miller, Hasterlik, and Finkel 1969).

Note well that these reports are *joint* from Argonne National Laboratory and the Argonne Cancer Research Hospital. The collaboration with the medical community of the University of Chicago and associated institutions was (and is) a very considerable contributory factor, not only in the analysis of the biomedical effects, but in the referral of cases, the retrieval of records, and insights into practices of the past.

The addition of a new group of dial painters was partly the result of a happy coincidence. The investigators knew there had been a Radium Dial Company plant in Ottawa, Illinois, and a Westclox plant in La Salle-Peru, Illinois, and that these had used luminous paint. But attempts to find a significant number of the luminizers were not fruitful. In 1955, long after other facets of the Argonne Radium Studies were well under way, a lady came to see Dr. Hasterlik for whole-body counting and skeletal radiographs. His suspicions were aroused,

and he asked her if she had ever handled radium or been a luminizer. She not only remembered being a dial painter but later provided Drs. Miller and Finkel with a photograph taken outside the factory,^(a) which is shown here as figure 1.8. Later, participants provided other photographs like the one shown in figure 1.9.



FIGURE 1.8. Group picture of dial painters at Ottawa, Illinois, plant taken about 1924, which enabled identification and follow-up. (Courtesy of Drs. Asher J. Finkel and Charles E. Miller, formerly of the Argonne Radium Study.)

Most of these women lived in small towns along the Illinois River, such as Ottawa, Peru, and La Salle, and worked at the plants. The population was quite stable, and by luck the town offices had for many years listed peoples' occupations along with other statistics. Armed with the pictures and helped by the town records, Charles E. ("Chuck") Miller went about finding and interviewing. Each person contacted could usually name others from the picture and knew their status. Eventually he and his colleagues were able to identify ninety-four of the ninety-eight individuals in the group prints! All but two of the individuals involved were traced. Of these, forty-three had died and forty-nine were still living; thirty-nine were considered in good health at a median age of seventy-one years. (The dial-painting jobs were frequently vacation fill-ins for high school students. Thus, the average age at exposure was quite young.) Sixteen of the dead and four of the living persons had had "radiogenic" lesions (Brues and Kirsh 1976).^(b)

(a) Drs. Finkel and Miller obtained the picture by visiting the lady's dressmaking shop.

(b) This paper is an excellent summary of the whole dial-painter saga as well as iatrogenic injections of radium for therapy.



FIGURE 1.9. Interior view showing dial painters at their desks in the Ottawa, Illinois, plant. This, too, helped in follow-up of the group. Note the open trays and close spacing of the workers. (Courtesy of Drs. Asher J. Finkel and Charles E. Miller, formerly of the Argonne Radium Study.)

The Elgin State Hospital group numbered only about thirty cases (but with the advantage of known doses and long follow-up). Therefore, the careful “detective” work of Miller and colleagues added substantially to the scope and validity of the Argonne Radium Studies. The other iatrogenic and self-treated individuals, while undoubtedly numbering in the thousands, were, and are, difficult to find and are a less homogeneous group than any of the others. The total group numbered 293 radium-burdened persons with 208 from the radium industry.

Attempts to find and bring in other patients from the Chicago area have been frustrated by the advanced age and lack of records of the doctors still alive, some of whom not only admit but declare proudly that they gave “hundreds” or “thousands” of radium injections or prescribed radium or radon water. Their faith is attested to by the fact that they included themselves in the meting-out of the nostrum (Hasterlik 1980).

We will consider that the Argonne Radium Studies as originally defined terminated as an entity when the MIT and other groups were consolidated with them in the late 1960s. By that time, some points of similarity and some of difference were compared to what we have described for the MIT-MGH series. These are summarized below:

- a. The radiogenic lesions were qualitatively comparable to those seen in the luminizers and patients from New Jersey, Connecticut, Massachusetts, and so forth, but there seem to be relatively more carcinomas of the sinus and

mastoid regions—especially at later times. This difference, if true, may reside in the absence of MsTh,^(a) for the iatrogenic patients received pure ^{226}Ra , and the luminous compound used at Ottawa had no MsTh in it.

- b. The ANL work, as will be noted, presents the results as radium body burdens—either the estimated maximum burden or the current or preterminal burden—not as calculated radiation dose. The ANL group felt that they could measure body burden accurately, but they eschewed the calculation of radiation dose. They did not like the necessity of delineating critical tissues, critical volumes, and the site of malignant transformation. Since no mesothorium was present in their cases, they were not forced, as was the MIT group, to devise a unit that would present cumulative radiation insult for persons with very different MsTh/Ra ratios. Thus, radiation dose could reasonably be expected to parallel radium burden in the ANL-ACRH cases. Nevertheless, it is awkward to have the two major studies of the day in this very important area use different ways of expressing dose. (Very recently this has changed.)
- c. The dose-response relationship as given for malignant tumors and blood dyscrasias shows an apparent threshold at about $1.2\ \mu\text{Ci}$ estimated maximum radium burden and at a somewhat lower point on the basis of current or preterminal burden. Figure 1.10 reproduces the relationship to estimated maximum radium burden, and figure 1.11 does the same for current or preterminal radium burden. There were 205 suitable cases for figure 1.10 and 218 for figure 1.11. The data points represent blocks of progressively increasing radium burden.

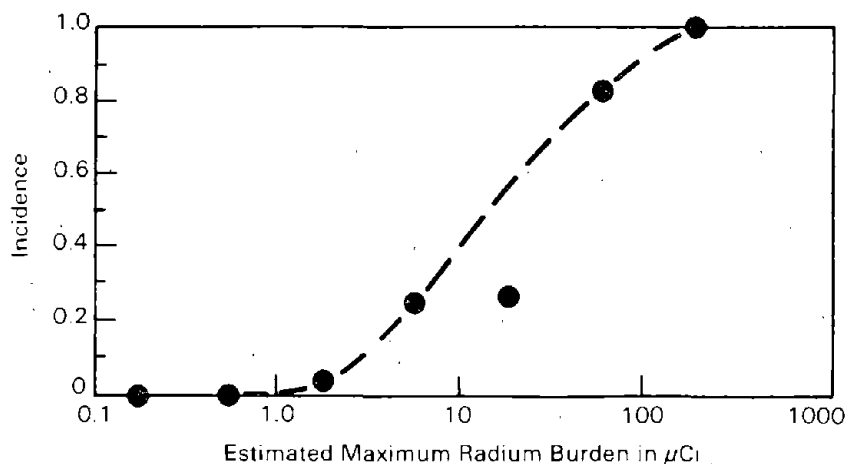


FIGURE 1.10. Incidence of radium-induced malignant tumors and blood dyscrasias in ANL-ACRH series as of September 1967. The incidence is plotted against estimated maximum radium burden in microcuries. Each point represents a block of progressively increasing average maximum radium burden for the subgroups. (Redrawn from Finkel, Miller, and Hasterlik 1969b, p. 222. Reprinted with permission of University of Utah Press, Salt Lake City, copyright 1969.)

(a) ... and its daughters.

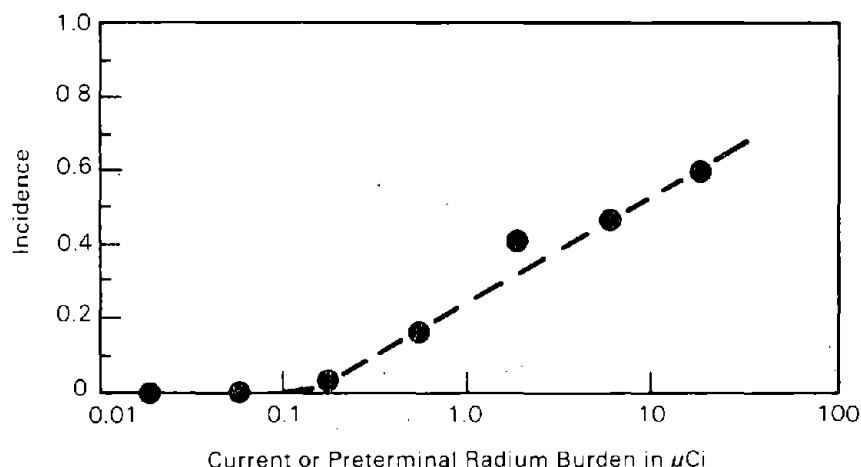


FIGURE 1.11. Incidence of radium-induced malignant tumors and blood dyscrasias in ANL-ACRH series as of September 1967. The incidence is plotted against the current or preterminal body burdens measured in each case. The points represent blocks of progressively increasing average radium burdens for the subgroups. (Redrawn from Finkel, Miller, and Hasterlik 1969b, p. 220. Reprinted with permission of University of Utah Press, Salt Lake City, copyright 1969.)

- d. It will be noted that, while there is an apparent threshold, as in the MIT studies,^(a) there is a continuous rise in incidence to 100% in figure 1.10 and no indication of the plateau seen in the MIT cases at about 30% incidence. The apparent difference between the ANL and MGH work in the incidence of tumors above the "threshold" cannot be clarified at this point. It may or may not be real, as will be discussed in the next section. The fact that a threshold, or a practical threshold, appears in both studies is noteworthy.
- e. The ANL reports do not emphasize the x-ray score or plot their data in terms of it. Yet it is clear that they used the system, since it was worked out with great care among the pathologists at the laboratories concerned. Clearly, the roentgenographic changes were given much the same weight in the two studies. Also, many general medical conditions, including such things as gait, an indication of bone destruction in areas such as the hip, were not likely to go unnoticed.
- f. The ANL work discusses epidemiologic bias but does not appear to make formal judgments regarding the epidemiologic suitability of each case or indicate that any have been omitted for this reason. (It does omit those

(a) Evans has calculated the radiation dose associated with the threshold in the residual body burden curve of figure 1.11 as about 2,000 rad. In view of the high M_sTh/Th ratio in the MIT cases, and the probable greater effectiveness rad for rad of M_sTh compared to ^{226}Ra , this figure may be considered in reasonable agreement with the "practical threshold" domain seen in the MIT work.

whose maximum burden could not be estimated even though they have a current burden.)

Further discussion of the work of this group postdates the organization of the Center for Human Radiobiology and will be taken up in the next section.

4. The Center for Human Radiobiology

As the time approached for Robley Evans to retire from full-time duties at MIT, there were in the summed MIT and ANL-ACRH studies some 850 persons identified, potentially exposed, and not yet studied. Additional potentially exposed persons were being identified through physician and hospital records, industrial employment records, and personal contacts. Because of the long life span of humans, a significant fraction of these would be expected to live into the twenty-first century. The great importance of maintaining full study of this invaluable resource led Evans to propose a consolidation of all of the work in a single center. There was detailed consideration of the long-range needs among all concerned including the Division of Biology and Medicine of AEC, the AEC Advisory Committee for Biology and Medicine, the Commissioners of AEC, and the Joint Committee on Atomic Energy of the Congress. The decision was to establish such a center under the title "Center for Human Radiobiology" and place it in the Radiological Physics Division of the Argonne National Laboratory. Dr. Robert E. Rowland was appointed as the first director. Andrew Stehney, Henry Lucas, Patricia Failla, Art Keane, and others identified with the radium work helped to staff the new organization. A field station was maintained at MIT, along with the counting facilities, and another at Phoenix, Arizona, where Dr. Evans made his principal domicile after retirement, and where Mary Margaret Shanahan went also. Others were established in New Jersey and Connecticut to maintain easy contact with the populations of interest. The populations continued to be identified separately, but the overall analysis of data and the central files resided at ANL. Austin Brues moved into the Center on his retirement from the Biology Division. Many others have joined. Unfortunately, Asher Finkel, Robert Hasterlik, and Charles Miller, the principal architects of the Argonne Radium Studies, moved out to other positions. The work of the Center began officially on September 1, 1970, although consolidation moves began somewhat earlier. All new data and new analyses of old data are now reported through the Center (1985).

The work done so far has involved mainly ^{226}Ra and ^{228}Ra , although the Center has had interests also in the ^{224}Ra patients, the Thorotrast patients, and others to be discussed subsequently. The broad name for the Center could subsume most of the efforts in human radiation epidemiology, e.g., plutonium workers, uranium workers, even the populations that received external radiation. However, this has not occurred and may never develop. There continue to be many separate enterprises for these other areas, manned by different groups and somewhat disparate in operation. There is coordination at the Washington level and good communication but no grand consolidation.

Most of the really critical results of work from this Center could be well beyond the cutoff date for this historical review. But a few points of interest can be made now:

- a. It appears that the radium results will be reported both in terms of the radium burden, particularly the initial radium burden calculated from measurements of current or preterminal burden, and in calculated cumulative rad.

- b. Epidemiologic methods of analysis comparable to studies with other types of radiation are being pressed. These include attempts to separate out for analysis groups whose names were obtained through sources largely unrelated to the presence of effects, i.e., were "epidemiologically suitable" in the terminology used earlier by Evans.
- c. Dose-response relationships are being drawn from the combined population and from segments thereof.
- d. Enough carcinomas are now appearing to allow formal comparison of their incidence properties with those of the sarcomas. Recently, many more carcinomas have appeared in those receiving pure radium than in the earlier years.
- e. The objective of having an almost "immortal" organization for following these invaluable cases to conclusion seems reasonably well protected. But it will require constant vigilance and aggressive protection of funding to keep the changing agencies who supply the support from forgetting the absolutely crucial importance of completing the radium saga.

The selected papers outlined below give the flavor of activities in the Center up to the close of the period of our interests.

Rowland et al. (1971) present a dose-response function for fifty-one sarcomas from a mixed population with the form:

$$\text{Incidence} = KD^2e^{-D/D_0}$$

where D is the average skeletal dose in rad to the time of diagnosis (*not* the dose to time of death as employed in earlier reports) and D_0 is 4,700 rad, the apparent threshold. The carcinoma incidence could not be fitted by any continuous function. An earlier report using the quantity of radium initially acquired gave reasonable fits for both types of tumors. But there were more carcinomas in the later analysis, and it should be more reliable.

The appearance times of the sarcomas increase with decreasing initial dose (Rowland, Keane, and Failla 1971) in line with the relationships pointed out earlier by Evans. On the other hand, appearance times of carcinomas do not seem to be related to initial burden.

In further work, the Center has gone to more homogeneous groups. This was made possible by the gradual accrual of more measured cases. For example, Rowland, Stehney, and Lucas (1977) report on a reasonably homogeneous group of female dial workers using radium burden rather than rad as the measure of dose because some had $MsTh$. Among other things, they conclude that linear functions do not describe the dose-response relationship here any better than in the less homogeneous group. A dose-squared exponential of the type described above works best for sarcoma incidence. The head carcinomas were equally well (and reasonably adequately) described by either a linear or a linear-quadratic exponential function. They announced their goal of adding as many more suitable cases to the group as possible.

Other recent papers from the Center have addressed survival time of these same workers using life table bases. (Stehney, Lucas, and Rowland 1978; Polednak, Stehney, and Rowland 1978). Here there are significant increases in modalities other than bone sarcoma, such as leukemia in the earlier years, but mortality ratios from all causes are greater than 1.0 only in the higher-intake groups. In the lower-dose group, the only cause category with a significantly greater number of observed than expected deaths was cancer of the colon. Is this radiation-related?

We can undoubtedly expect further and more detailed work-over of the accumulated data as the Center's work continues. It will require great care to resist the temptation to lump together cases that are really different in order to improve the statistical base.

5. Animal Studies at Argonne

Work with animals continued at ANL on a broad basis after World War II. Although some of it touches on our understanding of radium metabolism and effects, most is pertinent to comparative toxicology of the actinides, fundamental aspects of oncogenesis, or the basis for modeling of bone minerals. Each of these is more pertinent to other chapters of this compendium, and discussion will be deferred.

One paper describing a major radium toxicity study is that of M. Finkel, Biskis, and Jinkins (1969). They conducted experiments with 3,210 CF1 female mice given single intravenous injections. The mice were permitted to live until moribund, each mouse underwent thorough roentgenographic and post-mortem examination, both gross and microscopic. In a later, more extensive radium experiment, radiographic changes were the chief criterion beyond tumor incidence.^(a) The doses covered a wide range. As expected, bone damage and osteogenic sarcoma were the most prominent effects. Interestingly, the bone sarcoma was the most sensitive indicator of damage as compared to other measures. This may contrast somewhat with early bone changes seen roentgenologically in humans without sarcoma development.

There were 711 osteosarcomas in the experiment with some variation in site according to dosage level. Many other tumors appeared, but their incidence was not related to radium dose, and they were therefore not considered radiogenic. The incidence of osteosarcoma was linear with dose leading to the possibility of calculating tumor expectancy for comparison with other species, including man.

The dose-response relationship over the entire range showed sharp changes in slope at 2.5 $\mu\text{Ci/kg}$ and at 20 $\mu\text{Ci/kg}$. The relation appears to be linear between 0 and 2.5 $\mu\text{Ci/kg}$. This contrasts with data from the low-dose domain in man.

D. Other Postwar Radium Research

1. The Utah Beagle Experiment

The philosophy and genesis of this major experiment is described in chapters 7 and 8. Of special pertinence to the ideas considered in this chapter is the information on mesothorium toxicity. Because of the important role of MsTh in the dial painters, it was introduced into the Utah experiment for direct comparison to ^{226}Ra . The results are now reasonably complete. There is no doubt that the shorter-half-life isotope of radium, ^{228}Ra , i.e., mesothorium, is a more effective carcinogenic agent, rad for rad or microcurie for microcurie, by a factor of two to three. The explanation probably lies in the proportion of energy expended on bone surfaces. Even though ^{228}Ra is basically a mineral seeker, all

(a) This later experiment was initiated partly to take advantage of improved animal care facilities and decrease of intercurrent respiratory infections. The bone tumor incidence was higher per unit dose than in the early experiment, perhaps because the decrease in intercurrent infections cleared the way for expression of the cancers.

radium isotopes reside initially in part on bone surfaces and only gradually move into the mineral phase by exchange with calcium. Because of shorter half-lives, ^{228}Ra and its daughters expend a larger portion of their energy near the endothelial cells near to the bone surface. These cells are thought to be one of the prime targets in oncogenesis by bone-seeking radionuclides. Furthermore, ^{228}Th is formed from ^{228}Ra . Thorium is a surface seeker. Any ^{228}Th formed will remain at the surface or be translocated to bone surface. Finally, the ^{224}Ra formed next in the decay series has a relatively short half-life and, being formed in large part at the bone surface, will also expend a considerable part of its energy near the target cells. Thus, at least a qualitative explanation appears for the greater effectiveness of MsTh on a rad-for-rad basis and for the important role of MsTh when present in the dial painters.

Another interesting finding in the radium portion of the Utah beagle experiment is the production of intraocular melanomas from ^{226}Ra and ^{228}Ra (Taylor et al. 1969). The latent periods were long. This is reminiscent of the ocular changes described by Norris in his animals in the Plutonium Project work (see section V B). It has not appeared in man.

2. The Davis Beagle Study

A second major beagle study was initiated at the University of California at Davis in the mid-1950s. This experiment was designed primarily to evaluate the relative toxicity of ^{226}Ra to ^{90}Sr . The dosage levels of ^{226}Ra were similar to those employed in the Utah study. But the dose was divided into eight equal semi-monthly intravenous injections to simulate more closely the human exposure situations. Since the Radiobiology Laboratory work at Davis used radium primarily as a bench mark, and the comparative approach was paramount, further discussion will be postponed to later chapters.

3. The New Jersey Dial Painters

For a while during the 1950s, separate financing was provided by AEC through its New York Operations Office (NYO) for follow-up of the classic population of luminizers in New Jersey. This, called the "Radium Research Project," resided in the Department of Health of the State of New Jersey. This department had been interested in the subject from the very start as described in section III. The project director was Samuel C. Ingraham II, M.D. Among the collaborators was Theodore Blum, who helped to start the whole radium saga, although he died quite soon after the project started. Some films taken by Blum and by Martland are included in the analysis.

The object seemed to be epidemiologic follow-up. This undertaking was during the days of rapid multiplication of projects under AEC and appears to have been organized primarily to give the original New Jersey group an identity of their own. However, the publications from this group are not numerous. I find only two, an atlas of roentgenographic findings (Barrer et al. 1963), which gives no bibliographic references to other publications, and a report from the New York Operations Office of the AEC (NYO-2181-3). Roentgenographic findings are presented in detail for sixteen cases. While there are probably other publications of the same sort, it was not long before the New Jersey cases were being described again in the MIT reports as they had been in earlier years. Thus, it appears that the period of independence was not long enough to carry forward a full-blown epidemiologic study. The New Jersey cases seem to be adequately

described in the MIT reports, although the MIT group would be the first to say they had not attempted a formal epidemiologic approach.

4. Luminizers in Czechoslovakia

Jan Müller (1970) has reported on a population of luminizers in Prague and vicinity. This group used primarily a paint containing ^{90}Sr and its daughter product ^{90}Y . But prior to this, there was some use of a paint containing ^{226}Ra .

Under the auspices of the International Atomic Energy Agency, Müller has measured body burdens of both ^{90}Sr - ^{90}Y and ^{226}Ra using both urinalysis and whole-body counting. In contrast to most other studies, his concentrated on hematological changes with special emphasis on chromosome aberrations and their possible significance in leukemogenesis. Since the principal thrust of this study is on strontium, details will be reserved for chapters 8 and 13.

5. On "Hot Spots," Micro- and Macrodistribution

As individual samples of bone began to come in from autopsy and exhumation cases, it became apparent that the radium content was not the same in different bones. This fact was evident even in pre-World-War-II days as already described, but the story expanded considerably in later years. For example, the long bones lose radium at a slower rate than the skeleton as a whole and, thus, have higher contents long after administration. The specific activity in the vertebrae is different from that in the skeleton as a whole. This has a direct bearing, of course, on the calculation of dose and correlation of dose with site of tumor formation or other skeletal change. Examples are shown in the MIT annual reports (MIT 1965, 1966, 1967, 1968). The same phenomenon has been found in other populations and in the animal work. But tumor incidence does not seem to be correlated well with these differences in macrodistribution, and the average dose to skeleton has been applied in general use (see also chapter 16).

A second variation is in microdistribution. As soon as the technique of autoradiography became well established, and microscopic sections of bone could be viewed by both the conventional light microscope and by the picture the deposited radioisotopes made on special thin photographic films applied to the sections, it was apparent that there were areas of higher concentration and areas of more or less background concentration. The former were termed "hot spots." The relation of these to dosimetry had been discussed and tested widely. Also, investigation of the meaning of these variations in microdistribution to the mineral metabolism of bone has led to a whole new domain in the physiology and biochemistry of bone.

Suffice it now to refer the reader to a comprehensive review of alkaline earth metabolism in bone prepared by a task group of the International Commission on Radiological Protection (ICRP) under the chairmanship of John Marshall, Argonne National Laboratory. It was published as both ICRP Publication 20 (ICRP 1972) and in the journal *Health Physics* in 1972 (Marshall et al. 1973).

6. Radium Content of Water, Food, and of Individuals with No Known Occupational Exposure

Interest in the normal radium content of unexposed individuals and of their food and water supplies began in earnest in the late 1940s. Two reasons can be cited as paramount. First, as the knowledge of effects in occupationally exposed

individuals accumulated, it was natural to speculate on what concentrations might be present in persons with no known exposure, especially to see if they approached the levels at which effects occurred in the workers. Second, it became necessary to suggest factors by which the occupational limits should be reduced when large populations were concerned. A factor of ten to one hundred was suggested, which would have meant concentrations of 4 or $0.4 \mu\text{Ci/l}^{(a)}$ of water.

As early as 1934, Botstet had reported on the radium content of natural waters in the Pittsburgh area, and in 1939 and 1942, Krebs, who worked at the Kaiser-Wilhelm Institut für Biophysik, Frankfurt a. M., gave figures for both the waters of Frankfurt, Germany, and for humans and animals living in the area (Botstet 1934; Krebs 1939, 1942). Leo Marinelli in his Janeway Lecture (Marinelli 1958) pointed out that the possible population limits in water are lower than the radium contents reported for the Frankfurt and Pittsburgh water supplies. Hursh and Gates (1950) point out in addition that the upper range of Krebs's figures for body burden (in eighteen deceased individuals) is within 40% of the recommended maximum permissible body content for *occupational* exposure.

To check on the older figures, Hursh and Gates analyzed the bodies of twenty-five adult individuals (cadavers from the Rochester Medical School anatomy course) and six stillborn infants. The procedure of ashing the whole body and measuring the radium by collection of radon was superior to the in-vivo measurements possible at the time on unexposed individuals (i.e., it was before the whole-body counter was perfected). The measurements of Hursh and Gates showed only about 1/100 of the average value reported by Krebs,^(b) i.e., about 1.2×10^{-10} g versus Krebs's figure of 1.4×10^{-8} g average.

This finding led Hursh to an extensive and systematic study of the radium content of drinking water supplies from communities around the United States. Were the European waters enough higher to account for the factor of one hundred difference between their figures and those of Krebs? Carboys were shipped to forty-one cities representing about one-fifth of the population of the United States and were returned to the Rochester Laboratory for measurement. A few of the results are given in the Hursh and Gates paper cited; more are shown in a University of Rochester Atomic Energy Project Report published in 1953 (Hursh 1953). The average value was only $0.04 \mu\text{Ci/l}$.

Although some areas of Germany, like some areas in the United States, do have water with much higher radium content than the average, and Frankfurt is not far from one such area (Badgastein), it seems unlikely that the Krebs body-burden findings are correct.^(c)

(a) We would now use picocuries (pCi) as the unit.

(b) The paper by Hursh and Gates is replete with details not only of methodology but of possible correlations and extrapolations and is highly recommended as an example of how good internal emitter research should be done and reported.

(c) Since Krebs moved to the Army Medical Field Research Laboratory at Fort Knox, Kentucky, at about this time, any rechecks had to depend on the work of others. In a personal memorandum written October 28, 1949, Krebs states that Janitzky and coworkers had checked the radium activity of Frankfurt water at 0.3 to 0.5×10^{-12} g/g in contrast to the Hursh figures of about 10^{-16} g/g water. So there may be a real difference in the radium content, but it is not clear that this difference can account for the differences in body burden reported.

The next step was, of course, to examine the contribution made by food. This was taken up in the United States by one of Dr. Hursh's students, Paul Shandley, and in Germany by Muth et al. and Rajewsky et al. (Shandley 1953; Muth et al. 1957; Rajewsky et al. 1957). The average for the United States diet was about $1 \mu\text{Ci/day}$, which Marinelli points out is consistent with the $1.6 \mu\text{Ci}$ derived by the Chicago group (Stehney and Lucas 1956) from analysis of excreta. The figures from Germany were higher by factors of around ten, which probably reflects the higher radium content of the environment. In either case, the contribution from food is obviously quite small.

A final consideration from these studies is what chance there is that the normal incidence of osteosarcoma in man comes from the radium burden derived from natural sources. This is reviewed by Hursh and Gates. With an average measured body content of about 1×10^{-10} g and the knowledge that 5×10^{-6} g can be associated with minimal skeletal changes, the ratio is about fifty thousand to one, a far cry from accounting for the natural incidence of bone cancer.

7. Examination of Areas with High Radium Content in Drinking Water

The existence of waters with high radium and radon contents has been known for many decades, in fact for over a century in the case of radon. Many of the spas of Europe and the United States are built around such sources. But the principal interest in these is the inhalation of radon gas. This will be discussed in chapter 3. Obviously, the water supply in such areas is frequently high in radium, and some attempts have been made to measure possible effects on the indigenous population. However, the population indigenous to the spas is too small and too heterogeneous to support a reliable study.

It was therefore of great interest when it became apparent that some Illinois communities in the vicinity of Chicago had been drinking waters for half a century close to, or above, the allowable population exposure for ^{226}Ra in water and that these had, in addition, some ^{228}Ra . The total population appeared to be potentially over 100,000 individuals. The interested staff at Argonne National Laboratory zeroed in on this opportunity first with careful measurements of the water and the body burdens, and second with searches for above-normal incidence of bone cancer. They (Lucas and Ilcewicz 1958) found that the drinking water supplied by deep wells of many small towns in about half the counties of Illinois was up to one hundred times above the average found by Hursh for larger city supplies. These figures were summarized by Marinelli (1958). The body burdens in Chicago, which uses water from Lake Michigan that is very low in radium, and in the small towns differed by a factor of about fifteen. The tumor-incidence figures showed some interesting trends, some beyond the standard error of one group compared to another. But on the whole these were not beyond the uncertainty of the basic incidence figures. This is partly due to the fact that only twenty-seven cases of bone cancer were uncovered by the survey. It was probably due also to the fact that the really high radium contents of water were in the smallest communities. Thus, the change in incidence, if any, is masked by the statistical uncertainties. Marinelli and others have urged addition of populations from neighboring states with similar geological formations. These, if added and studied carefully, could greatly improve the statistics, since the total population might then be over two million. But the changing times with greater population mobility even in small towns like those under study, and the enormous effort needed to do the job properly, seem to have discouraged significant further work. Not much new has appeared in the recent

literature. Other problems and other populations have come along to deflect the efforts of those concerned. Thus, the work, while bringing forth much interesting information, did not show the increase in bone cancer that many at first considered almost inevitable. It also shows that isolation of a single factor from among the many impinging on a population is a difficult and extremely demanding exercise.

The consideration of radium in water is inextricably linked to occurrence and possible effects of radon. For convenience, the possible exposures from radium-radon-containing waters at hot springs, spas, and related sources are taken up in chapter 3. In a sense, that discussion is an extension of that in the paragraphs above.

VII. Radium-224

A new domain in American biomedical research with the isotopes of radium, and one with a strong international flavor, began in the 1960s. All of our discussions so far in this chapter have concerned the most commonly employed isotope of radium, ^{226}Ra , and to some extent its decay products, plus some necessary consideration of ^{228}Ra because it occurred as a contaminant in the luminizing paint. The new domain concerns ^{224}Ra , a decay product of ^{228}Th . "Chuck" (Dr. Charles W.) Mays at the University of Utah had a German research assistant. One day she called his attention to some papers in the German literature she had seen in the library. They described the use by a country doctor of a nostrum called "Peteosthor"^(a) for the treatment of tuberculosis, ankylosing spondylitis, and related maladies in northern Germany. A young German pediatrician at the University Children's Clinic in Göttingen was asked in 1948 to investigate these treatments, partly because they involved many children. His name was Heinz Spiess. He found that the nostrum was useless for the diseases being treated, nor did it have any effect on tubercle bacilli in vitro except at very high concentrations (Spiess 1978). But already clinical signs of radium toxicity were showing in the patients.

Here, it seemed, was a whole new population distressingly similar to the thousands of individuals who had received ^{226}Ra for "therapy," but with a radium isotope of much shorter half-life, only 3.6 days. Mays wrote immediately to Spiess for reprints. Bob Rowland at Argonne Laboratory had the Spiess work translated and circulated in the ANL translation report series. Mays invited Spiess to present his findings at the next Sun Valley symposium sponsored by the Utah project to be held in September 1967. Spiess came and delivered, in excellent English, a superb summary of the biomedical effects and the characteristics of the population (Spiess 1969), which was something of a bombshell. It was entirely new information to most of the audience.

But the project needed some help with dosimetry and physical problems. So Mays, the physicist turned biophysicist, went to Germany for a month between meetings he was already scheduled to attend in Europe. Thus started a collaboration that has flourished ever since with yearly visits between Salt Lake City and Munich, where Spiess had moved soon after the work was well established. To a

(a) The preparation was a combination of ^{224}Ra , colloidal platinum, and eosin. The platinum and eosin were alleged to facilitate access of the therapeutic agent, ^{224}Ra , to the areas of inflammation and thus action on the tubercle bacillus itself. It was prepared by the Buehler firm in Braunschweig, Germany.

degree, we saw here a repeat of the physicist-biologist-physician collaboration that worked so well in operating the MIT project, and indeed in numerous AEC laboratories during the postwar years.

The story has been told well in readily available literature already cited, including a narrative historical summary by Spiess (1978). Hence, we will present primarily a summary-type review.

A. The Population

The injection of ^{224}Ra (Th-X) occurred in the years 1944 to 1951 in hospitals primarily in northern Germany, especially one at Hildesheim presided over by a Dr. Troch, who was championing Peteosthor. The patients ranged in age from one to seventy years. The total number in the original group was about 2,000; of these, 802 had been checked at the time of Spiess's Sun Valley paper; 206 of these were youths under twenty-one years old. A 1980 summary of the results is given in tables 1.2 and 1.3 prepared by Mays (1980).

TABLE 1.2. Summary of ^{224}Ra Patients in the Spiess Follow-Up—Average Date of Injection, About 1950

	Age at First Treatment		
	1-20 Years	Adult	Total
Total traced patients	218	680	898
Deaths	77	333	410
Bone sarcomas	36	18	54
Cancers of soft tissue	9	54	63
Leukemias	0	3	3
Panmyelosis or "anemia"	1	4	5
Kidney diseases	6	49	55
Liver diseases	1	19	20
Exostoses (benign)	28	0	28
Teeth breaking off	23	13	36
Cataracts	11	25	36

Source: Reset from Mays 1980.

Since the nostrum was prescribed for the treatment of tuberculosis, and some of the war and early postwar years are involved, we would expect to find a large number of younger patients, as indeed was the case. This, plus the generally poor nutritional status of the population, particularly at the outset of treatments, makes this set of cases qualitatively different from the dial painters and iatrogenic cases in the United States. But the analysis seems to have been able to cope quite adequately with this difference. Indeed, it adds many points of special interest because of the opportunity to see effects on growing bone and in a young population.

The use of ^{224}Ra in children was stopped about 1951, and for all forms of tuberculosis soon thereafter. But the population is available for long-term study.

Radium-224 continues to be used in Germany but is now limited largely to patients with ankylosing spondylitis and to use of pure ^{224}Ra . (This malady is treated in England by x rays and has provided another population for study

TABLE 1.3. New Cases Between 1974 and 1980

	Age at First Treatment		
	1-20 Years	Adult	Total
(Total living and dead patients)	(218)	(680)	(898)
Deaths during the last 6 years	11	83	94
Bone sarcoma cases	0	0	0
Cancers of soft tissue	4	16	20
Leukemias	0	0	0
Panmyelosis or "anemia"	0	0	0
Kidney diseases	2	16	18
Liver diseases	0	1	1
Exostoses (benign)	0	0	0
Teeth breaking off	6	6	12
Cataracts	4	12	16

Source: Reset from Mays 1980.

outside the scope of this book.) The current doses are, however, much smaller than those given earlier (Schaes 1978), and toxic effects will probably be much less evident.

The observation period of the initial population is now about thirty years.

B. The Dosages

Multiple injections were given of from 8 to 70 μCi each. Total amounts were 40 to 5,000 μCi . The duration of injections was from a few weeks to a few years.

The medical records of the patients give the alpha-particle ionization of ^{224}Ra and its daughter products in an old unit, esE (*elektrostatichen Einheiten*), whose translation to microcuries required considerable work (Spiess and Mays 1970). By acquiring sample injection solutions from the same firm made by the same techniques of separation as those injected into the patients, they were able to establish a working relationship:

$$1,000 \text{ esE (stated)} = 140 \mu\text{Ci } ^{224}\text{Ra (injected)}$$

Another problem was the conversion to skeletal and local dose in rad, which the investigators felt compelled to do in order to compare effects in different age groups, growing skeletons versus mature skeletons, etc. Some of the subjects grew considerably during the period of their injections, and it was necessary to apply growth statistics from standard growth tables for German children unless individual data were at hand. The ICRP's "Standard Man" was not applicable to these situations.

Further, there arose the question of what mass to compute the dose over. Radium-224 is metabolized chemically like all radium isotopes. The patterns described earlier for ^{226}Ra hold just as well for it. Thus, the early deposition is in soft tissues and on the surfaces of bone. Later it leaves the soft tissues, and gradually the surface deposits in bone migrate into bone mineral. But because of its much shorter half-life, a higher portion of the energy imparted to tissue by ^{224}Ra is in the surface layers of bone, i.e., the endosteal cells, and in soft tissues in general. Spiess and Mays (1973) contend that the suitable critical tissue or critical volume must be the bone surfaces. On this basis, the rad dose to bone surfaces from ^{224}Ra is about nine times that based on average skeletal dose, which is used for expressing dose from ^{226}Ra .

In terms of relative effectiveness using the same base for calculation (i.e., average skeletal dose), Spiess and Mays (1970) calculate that the lowest skeletal dose causing death with ^{224}Ra is only 90 rad compared to about 1,200 rad for the dial painters (see section VI B).

Plots of the dose-response relationship for bone sarcoma appear to be linear, and this has allowed Mays to make risk estimates from the data. But the range of data and scarcity of sarcomas in the lowest dose domains do not allow a reliable distinction between a linear nonthreshold relation and others, including a "practical threshold," at low doses.

C. The Effects

Bone tumor incidence is high in the ^{224}Ra population (cf. table 1.2). The doses are high and quite effective. If one uses average skeletal dose, ^{224}Ra is much more effective than ^{226}Ra , but if one uses the relative endosteal-cell doses, the effectiveness of ^{224}Ra more nearly equals that of ^{226}Ra , or at least is close to the error of the measurements (a factor of thirteen versus a factor of nine).

In addition to production of cancers, there is marked growth retardation, presumably due to inhibition of bone growth, tooth breakage and other dental problems, and the array of roentgenographic changes described earlier for ^{226}Ra , e.g., damage to epiphyseal cartilage, growth-arrest plates, changes in spongiosa, and irregular ossification. Also, there seem to be many benign osteochondromas.

It is clear that these cases show many more effects in soft tissue than does ^{226}Ra (Spiess, Gerspach, and Mays 1978). These include kidney disease, soft-tissue neoplasms of considerable variety, and possibly liver damage (although hepatitis was endemic in the hospitals, and this is therefore not clear-cut). Also cataracts appear in considerable number and include many individuals in the age group where spontaneous cataract is very rare. It seems unlikely that the soft-tissue neoplasms are radiation-induced. The problems with the liver changes have been mentioned, but both these and the kidney changes are a function of dose. The cataract incidence is so unusual that it appears clearly to be associated with the therapy.

D. On the Effect of Dose Protraction

In an interesting paper given at the Hanford symposium, Radionuclide Carcinogenesis, in May 1972, Spiess and Mays (1973) present calculations that they conclude show that protraction of dose *increases* the effectiveness of ^{224}Ra . This is exactly the opposite of the usual effect seen with x rays and other low-LET (linear energy transfer) radiation. It also differs from that described for some non-bone-seeking alpha emitters such as ^{210}Po (Stannard, Blair, and Baxter 1964; Stannard 1973). While Spiess and Mays offer several plausible explanations, and it has been confirmed in animal experiments (Müller et al. 1978), the phenomenon requires further study, particularly in view of its important bearing on standard setting.^(a)

E. Comment

Research with ^{224}Ra is continuing quite actively. This is partly because it is involved in the Thorotrast cases to be discussed in chapter 4, as well as in its

(a) More recent work confirms and extends these observations.

own right. Some recent papers are cited below. In 1974, an international symposium on ^{224}Ra and Thorotrast was held at Alta, Utah. Its published papers occupy an entire issue of *Health Physics* (Vol. 35, Number 1, July 1978). In addition to the papers by Spiess et al. and Müller et al., there are discussions of the history of the use of ^{224}Ra , its radioactive properties and biological behavior, preparation of solutions, and so forth.

Spiess and Mays (1979) have described the liver diseases in detail and shown a marked contrast between ^{224}Ra and Thorotrast.

Clearly, this recent addition to the scope of radium research has provided valuable new information and valuable opportunities to test ideas developed earlier. It is an active current field internationally and should be followed carefully by the interested reader.

Mays (1980) has prepared an informative chronology of the development of the story of ^{224}Ra ; it is shown below as table 1.4. Note the several items we could not discuss here.

TABLE 1.4. Some Dates in the History of ^{224}Ra

1902	— Thorium-X (^{224}Ra) discovered by Soddy and Rutherford.
1912	— Arthritis patient died because of ^{224}Ra injections.
1944	— Radium-224 therapy of TB and Ank. Spond. started by Troch.
1948	— Heinz Spiess asked to investigate ^{224}Ra therapy. ^{224}Ra deposition same for "Peteosthor" or pure ^{224}Ra .
1949	— Spiess showed Peteosthor ineffective against TB.
1950	— Spiess officially protested against Peteosthor.
1951	— Peteosthor stopped in children and TB adults. Treatment of Ank. Spond. continued, but with pure ^{224}Ra .
1952	— Spiess began first follow-up.
1956	— Spiess published the first bone sarcoma cases.
1963	— Radium-224 injected into 14 beagles, University of Utah.
1964	— C. W. Mays learned of Spiess results.
1967	— Spiess presented results at Sun Valley Symposium.
1969	— Mays began annual work sessions with Spiess. Converted esE to μCi (1000 esE = 140 μCi ^{224}Ra). Calc. av. skel. dose (1 μCi ^{224}Ra \rightarrow 14 rad to adults).
1970	— Spiess and Mays published their results in <i>Health Physics</i> . Radium-224 therapy became less frequent. Hug and Schales began new study of additional patients.
1972	— Radium-224 effectiveness increased with protraction in man.
1974	— Alta Symposium: Protraction effect confirmed in mice. Skeletal effects and soft tissue effects presented. John Marshall calculated endosteal dose to adults.
1975	— Radium-224 results used to predict ^{239}Pu risk to bone.
1976	— Neuherberg Symposium: Benefit and risk of therapy. Similar appearance times for bone sarcoma and leukemia.
1977	— Gossner and Wick continue the studies of Hug and Schales. DOE approved the injection of 126 beagles with ^{224}Ra , University of Utah.
1978	— Radium-224 injected into 120 mice at University of Utah.
1979	— In \sim 1000 new low-dose patients, 2 skeletal sarcomas found by R. Wick versus a life-span prediction of 3 cases based on the linear model of Spiess and Mays for an injection span of 2 months.
1980	— No new bone sarcomas since 1974. Soft tissue cancers are increasing. No new leukemias since 1957. Kidney diseases are increasing. Tooth breakage is increasing. Cataracts are increasing. What is the effect of the platinum in the "Peteosthor"?

Source: Reset from Mays 1980.

The ^{224}Ra data have recently contributed to estimation of risk from plutonium in man (cf. later chapters).

VIII. Summary and Commentary

Radium, primarily ^{226}Ra , has been a source of healing and palliation of cancer and other ills since not long after its isolation from pitchblende by Marie Curie. The number of human beings and animals benefited by the penetrating gamma radiations from radium exceed by far the number harmed by the effects of radium taken internally. Nevertheless, it is this latter aspect, the effects of the highly ionizing alpha particles inside of cells and tissues, that comes within the purview of this chapter and this book.

Unlike x rays, whose potential for harm became apparent very soon, it was not until the 1920s, through the dolorous story of the luminous dial painters from World War I and the numerous individuals who took or received radium as a therapeutic nostrum, that the potential for lethal damage from deposited radium became apparent. At the outset, there was the fortunate, indeed extraordinary, series of coincidences in the meeting of a perceptive dentist (Blum), conscientious and talented physicians (Martland and Hoffman), a good chemist (Gettler), and, later, a dedicated and talented physicist (Evans) around the saga of the dial painters. However, the unraveling of cause and effect and quantitation of dose and effect is due largely to the life-long devotion of Robley Evans and his colleagues at the Massachusetts Institute of Technology, and, in more recent years, to investigators at the Argonne National Laboratory near Chicago (The Argonne Radium Studies and the Center for Human Radiobiology).

Through fortunate continuation of both interest and funding, the biomedical effects of radium in man represent our longest and most thorough set of observations of the effects of internally deposited radioactivity. The work must continue into the twenty-first century in order to study all of those with identifiable or strongly suspected body burdens of significance.

A maximum permissible body burden of radium for occupational exposure was set just before World War II and has remained viable ever since. For this and other reasons, radium became, and has remained, the bench mark for gauging the effects of many other radionuclides, especially those that deposit in bone.

By virtue of its position as a bench mark, radium was used in extensive animal experiments, both during World War II (primarily at Chicago and Rochester) and since (at Argonne National Laboratory, University of California at Davis, University of Utah, and similar large projects described in later chapters). In the process, much was learned about the metabolism (i.e., pharmacokinetics) of radium and of its effects that could not have been learned at the lower levels of intake characteristic of the experience with humans. Yet, despite enormous efforts in both clinical and experimental settings, there is still uncertainty regarding the details of the dose-response curve. Much of the clinical information points to a level below which bone cancer does not develop, but this does not mean that more subtle effects are absent.

Part of the problem has been that few of the occupational exposures and not all of the clinical cases involved pure ^{226}Ra . The majority had other isotopes of radium or some of the decay products mixed in. This made the dosimetry more complex. This, plus a lack of knowledge of the exact nature and location of the

cells at greatest risk for bone cancer development, means that resolution of detailed quantitative aspects will require yet some time and major advances in cancer biology.

A prominent feature of the research on radium has been the finding of new exposed populations. The growth and development of these is detailed in the chapter. One of the most prominent "new" populations was a group in Germany, primarily children found just after World War II, who had been given a shorter half-life isomer of radium, ^{224}Ra . The collaboration of German investigators and the group at the University of Utah (especially C. W. Mays) has produced a dosimetric and epidemiologic little brother to the work with ^{226}Ra , ^{228}Ra , and the other radionuclides involved with the dial painters, radium chemists, and many of the unfortunates who dosed themselves with preparations such as "Radithor."

There was naturally considerable interest in the amounts of radium and associated elements in water and in food. It soon became apparent that the amounts in water could vary over a wide range. Some well waters in the central United States and in Europe have concentrations far above the average. The waters of the various therapeutic spas are especially high. Yet, no clear relationship between health effects and exposure to or drinking of these waters has been demonstrable. The population sizes are too small and the exposure times to the highest concentrations too short. Nevertheless, there are those who advocate more formal and detailed study of these populations in the future.

Useful summaries, particularly of recent work, are included in the chapter. Particular note might be taken of Jee (1976), UNSCEAR (1977), and a partial summary of radium toxicity studies produced by the Bureau of Radiological Health, U.S. Public Health Service (Chiacchierini et al. 1970).

Radium could probably be categorized, as Peter Alexander once characterized x rays, as a "double-edged sword," i.e., a source of therapeutic value when used one way, a source of deleterious, even fatal, effects when used in another. In this case, it is the penetrating gamma radiation from sealed sources of radium that supports the genuine therapeutic uses of radium, while it is the short-range highly ionizing alpha particles that underlie the untoward effects of radium deposited in the body.

References(a)

- Angevine, E. 1979. *History of the National Consumers' League 1899-1979*. Sponsored by the National Endowment for the Humanities and the National Consumers' League. [Seen in manuscript form through the courtesy of John Villforth, Director, Bureau of Radiological Health, U.S. Food and Drug Administration (FDA), who had received it from W. Janssen, FDA Historian, Washington, D.C.]
- Aub, J. C., R. D. Evans, D. M. Gallagher, and D. M. Tibbetts. 1938. Effects of treatment on radium and calcium metabolism in the human body. *Ann. Intern. Med.* 11:1443-63.
- Aub, J. C., R. D. Evans, L. H. Hempelmann, and H. S. Martland. 1952. The late effects of internally-deposited radioactive materials in man. *Medicine* 31:221-329.
- Aub, J. C., L. T. Fairhall, A. S. Minot, and P. Reznikoff. 1926. *Lead poisoning*. Baltimore: Williams & Wilkins.
- Badash, L. 1979. *Radioactivity in America. Growth and decay of a science*. Baltimore: Johns Hopkins Univ. Press.

(a) References given here were gleaned in part from secondary sources, including summaries published over the last several decades, but most have been checked in the original source.

- Barker, H. H. and H. Schlundt. 1930. The detection, estimation and elimination of radium in living persons given radium chloride internally. II. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* 24:418-23.
- Barrer, L. A., C. B. Henle, R. Bonda, and H. W. Fisher. 1963. *Atlas of current roentgenographic findings in the New Jersey radium cases*. NYO-2761, Washington, D.C.: U.S. Atomic Energy Commission.
- Becquerel, H. 1896a. Emission de radiations nouvelles par l'uranium métallique. *C. R. Hebd. Séances Acad. Sci.* 122:1086-88.
- Becquerel, H. 1896b. Sur les propriétés différentes des radiations invisibles émises par les sels d'uranium, et du rayonnement de la paroi anticathodique d'un tube de Crookes. *C. R. Hebd. Séances Acad. Sci.* 122:762-67.
- Becquerel, H. 1896c. Sur les radiations émises par phosphorescence. *C. R. Hebd. Séances Acad. Sci.* 122:420-21.
- Becquerel, H. 1896d. Sur les radiations invisibles émises par les corps phosphorescents. *C. R. Hebd. Séances Acad. Sci.* 122:501-3.
- Becquerel, H. 1896e. Sur les radiations invisibles émises par les sels d'uranium. *C. R. Hebd. Séances Acad. Sci.* 122:689-94.
- Becquerel, H. 1896f. Sur quelques propriétés nouvelles des radiations invisibles émises par divers corps phosphorescents. *C. R. Hebd. Séances Acad. Sci.* 122:559-64.
- Bloom, W. 1948. *Histopathology of irradiation from external and internal sources*. National Nuclear Energy Series, div. IV, vol. 22, pt. 1. New York: McGraw-Hill.
- Blum, T. 1924. Osteomyelitis of the mandible and maxilla. Paper read before Am. Dental Assoc., September 1924. In *Mon. Labor Rev.* June 1929, p. 1222.
- Botstet, H.G. 1934. Radium content of some connate waters. *Physics* 5:276-80.
- Boyd, G. A., H. E. Silberstein, R. M. Fink, A. Frenkel, W. L. Minto, R. G. Metcalf, G. Casarett, and G. M. Suter. 1950a. Pilot studies on the intravenous lethal dosage of polonium, plutonium, and radium in rats. Chapter 7 in Fink 1950, pp. 211-94.
- Boyd, G. A., A. Williams, W. L. Minto, D. V. Tiedeman, R. M. Fink, G. Casarett, and R. G. Metcalf. 1950b. Simultaneous studies on the intravenous lethal dosage of polonium, plutonium, and radium in rats. Chapter 8 in Fink 1950, pp. 295-404.
- Brucer, M. 1979. Becquerel breaks the law. *Vignettes in nuclear medicine*, no. 94. St. Louis: Mallinckrodt.
- Brues, A. M. 1976. Malignancies in patients contaminated with radium. In Jee 1976, pp. 451-55.
- Brues, A. M. and I. E. Kirsh. 1976. The fate of individuals containing radium. *Trans. Am. Clin. Climatol. Assoc.* 88:211-18.
- Castle, W. B., K. R. Drinker, and C. K. Drinker. 1925. Necrosis of the jaw in workers employed in applying a luminous paint containing radium. *J. Ind. Hyg. Toxicol.* 7:371-82.
- Chiacchierini, R. P., G. L. Jessup, N. S. Nelson, N. C. Telles, E. Tompkins, and J. F. Wright. 1970. *A review of radium toxicity studies*. BRH-DBE 70-5. Washington, D.C.: Bureau of Radiological Health, U.S. Public Health Service, U.S. Department of Health, Education and Welfare.
- Cloutier, R. J. 1979. *Florence Kelley and the radium dial painters*. Paper presented at the 24th annual meeting of the Health Physics Society held in Philadelphia, July 1979. (Also Cloutier, R. J. 1980. Florence Kelley and the radium dial painters. *Health Phys.* 39:711-16.)
- Craver, L. F. and H. Schlundt. 1935. Parathyroid extract and viosterol treatment of radium poisoning. *J. Am. Med. Assoc.* 105:959-60.
- Curie, P., [Mme] P. Curie, and G. Bémont. 1898. Sur une nouvelle substance fortement radio-active, contenue dans la pechblende. *C. R. Hebd. Séances Acad. Sci.* 127:1215-17.
- Curie, P. and [Mme] S. Curie. 1898. Sur une substance nouvelle radio-active, contenue dans la pechblende. *C. R. Hebd. Séances Acad. Sci.* 127:175-78.
- Dubkov, A. A. 1940. The influence of radioactive elements on the yields of plants. *Bull. Acad. Sci. U.R.S.S., ser. biol.*: 783-801.

- Dubkov, A. A. 1941. Effect of radioactive elements (Ra) and rare earths (TR) upon yield and rubber content of KOK-Saghyz. *C. R. Hebd. Séances Acad. Sci. U.R.S.S.* 32:667-68.
- Dunlap, C. E., J. C. Aub, R. D. Evans, and R. S. Harris. 1944. Transplantable osteogenic sarcomas induced in rats by feeding radium. *Am. J. Pathol.* 20:1-21.
- Eisenbud, M. 1979. Taped interview, July 9, 1979.
- Evans, R. D. 1933. Radium poisoning: A review of present knowledge. *Am. J. Public Health* 23:1017-23.
- Evans, R. D. 1937. Radium poisoning. II. The quantitative determination of the radium content and radium elimination rate of living persons. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* 37:368-78.
- Evans, R. D. 1966. The effect of skeletally deposited alpha-ray emitters in man. *Br. J. Radiol.* 39:881-95.
- Evans, R. D. 1967. The radium standard for boneseekers—Evaluation of the data on radium patients and dial painters. *Health Phys.* 13:267-78.
- Evans, R. D. 1978a. Personal interview in Scottsdale, Ariz., April 27, 1978.
- Evans, R. D. 1978b. Videotape interview: Vignettes of early radiation workers. Rockville, Md.: U.S. Food and Drug Administration, Div. of Radiological Health.
- Evans, R. D., R. S. Harris, and J. W. M. Bunker. 1944. Radium metabolism in rats, and the production of osteogenic sarcoma by experimental radium poisoning. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* 52:353-73.
- Evans, R. D., A. T. Keane, and M. M. Shanahan. 1972. Radiogenic effects in man of long-term skeletal alpha-irradiation. In *Radiobiology of plutonium*, eds. B. J. Stover and W. S. S. Jee, pp. 431-68. Salt Lake City: J. W. Press.
- Fink, R. M. 1950. *Biological studies with polonium, radium, and plutonium*. National Nuclear Energy Series, div. VI, vol. 3. New York-Toronto-London: McGraw-Hill.
- Finkel, A. J., C. E. Miller, and R. J. Hasterlik. 1959. *Status report of study of long-term effects of radium in humans*. Semiannual report, ANL-6104, p. 87. Argonne, Ill.: Argonne National Laboratory.
- Finkel, A. J., C. E. Miller, and R. J. Hasterlik. 1969a. Radiobiological parameters in human cancers attributable to long-term radium deposition. In *Radiation-induced cancer*, SM-118/7, pp. 183-202. Proceedings of a symposium held in Athens, April 28-May 2, 1969. Vienna: International Atomic Energy Agency.
- Finkel, A. J., C. E. Miller, and R. J. Hasterlik. 1969b. Radium-induced malignant tumors in man. In *Delayed effects of bone-seeking radionuclides*, eds. C. W. Mays, W. S. S. Jee, R. D. Lloyd, B. J. Stover, J. H. Dougherty, and G. N. Taylor, pp. 195-225. Salt Lake City: Univ. of Utah Press.
- Finkel, M. P., B. O. Biskis, and P. B. Jenkins. 1969. Toxicity of radium-226 in mice. In *Radiation-induced cancer*, SM-118/11, pp. 369-91. Proceedings of a symposium held in Athens, April 28-May 2, 1969. Vienna: International Atomic Energy Agency.
- Flinn, F. B. 1931. Elimination of radium salts from the human body. *J. Am. Med. Assoc.* 96:1763-65.
- Flinn, F. B. 1934. Stimulating action of radio-active deposits in the body. *Radiology* 23:331-38.
- Flinn, F. B. and S. M. Seidlin. 1929. Parathormone in the treatment of "radium poisoning." A preliminary report. *Bull. Johns Hopkins Hosp.* 45:269-75.
- Hasterlik, R. J. 1980. Taped interview at La Jolla, Calif., April 28, 1980.
- Hasterlik, R. J., C. E. Miller, and A. J. Finkel. 1969. Radiographic development of skeletal lesions in man many years after acquisition of radium burden. *Radiology* 93:599-603.
- Hoecker, F. E. 1944a. The radon/carbon dioxide ratio as an index to excessive radium absorption. *J. Ind. Hyg. Toxicol.* 26:281-88.
- Hoecker, F. E. 1944b. The significance of absorbed radium as indicated by the coefficient of elimination. *J. Ind. Hyg. Toxicol.* 26:289-95.
- Hoffman, F. L. 1925. Radium (mesothorium) necrosis. *J. Am. Med. Assoc.* 85:961-65.
- Hunter, D. and J. C. Aub. 1927. Lead studies. XV. The effect of parathyroid hormone on the excretion of lead and of calcium in patients suffering from lead poisoning. *Q. J. Med.* 20:123-40.

- Hursh, J. B. 1953. *Radium content of public water supplies*. UR-257. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Hursh, J. B. and A. A. Gates. 1950. Body radium content of individuals with no known occupational exposure. *Nucleonics* 7(1):46-59.
- ICRP. See International Commission on Radiological Protection.
- International Commission on Radiological Protection. 1972. *Alkaline earth metabolism in adult man*. ICRP Pub. 20. Oxford: Pergamon Press.
- Jacobson, L. O. and E. L. Simmons. 1946. *Studies on the metabolism and toxic action of injected radium. II. The hematological effects of parenterally administered radium. A comparison of plutonium and radium effects*. AECD-2372. Manuscript dated June 1946, declassified November 1948. Washington, D.C.: U.S. Atomic Energy Commission.
- Jee, W. S. S. 1976. *The health effects of plutonium and radium*. Salt Lake City: J. W. Press.
- Krebs, A. 1939. Über die normale und abnormale Radioaktivität menschlichen und tierischen gewebes. *Fundam. Radiol.* 5:89-112.
- Krebs, A. 1942. Untersuchungen zum Problem der Radiumvergiftung. IV. Der Gesamt-radiumgehalt des menschlichen Organismus. *Strahlentherapie* 72:164-69.
- Looney, W. B., R. J. Hasterlik, A. M. Brues, and E. Skirmont. 1955. A clinical investigation of the chronic effects of radium salts administered therapeutically (1915-1931). *Am. J. Roentgenol. Radium Ther. Nucl. Med.* 73:1006-37.
- Lucas, H. F., Jr. and F. H. Ilcewicz. 1958. Natural radium 226 content of Illinois water supplies. *J. Am. Water Works Assoc.* 50:1523-32.
- Maletskos, C. J., A. G. Braun, M. M. Shanahan, and R. D. Evans. 1964. Quantitative evaluation of dose-response relationships in human beings with skeletal burdens of radium-226 and radium-228. In *Assessment of radioactivity in man*, vol. 2, pp. 225-52. Proceedings of a symposium held in Heidelberg, May 11-16, 1964. Vienna: International Atomic Energy Agency.
- Marinelli, L. D. 1958. Radioactivity and the human skeleton. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* 80:729-39.
- Marshall, J. H., E. L. Lloyd, J. Rundo, J. Liniecki, G. Marotti, C. W. Mays, H. A. Sissons, and W. S. Snyder. 1973. Alkaline earth metabolism in adult man. *Health Phys.* 24:125-221.
- Martland, H. S. 1925. *Some unrecognized dangers in the use and handling of radioactive substances, with especial reference to the storage of insoluble products of radium and mesothorium in the reticulo-endothelial system*. Read before the New York Pathological Society, October 8, 1925.
- Martland, H. S. 1929. Occupational poisoning in manufacture of luminous watch dials, general review of hazard caused by ingestion of luminous paint, with especial reference to the New Jersey cases. *J. Am. Med. Assoc.* 92:466-73, 552-59.
- Martland, H. S., P. Conlon, and J. P. Knef. 1925. Some unrecognized dangers in the use and handling of radioactive substances, with especial reference to the storage of insoluble products of radium and mesothorium in the reticulo-endothelial system. *J. Am. Med. Assoc.* 85:1769-76.
- Martland, H. S. and R. E. Humphries. 1929. Osteogenic sarcoma in dial painters using luminous paint. *Arch. Pathol.* 7:406-17.
- Massachusetts Institute of Technology. 1959. *Radium and mesothorium poisoning and dosimetry and instrumentation techniques in applied radioactivity*. Annual Progress Report. Cambridge, Mass.
- Massachusetts Institute of Technology. 1961. *Radium and mesothorium poisoning and dosimetry and instrumentation techniques in applied radioactivity*. Annual Progress Report. Cambridge, Mass.
- Massachusetts Institute of Technology. 1965. *Radium and mesothorium poisoning and dosimetry and instrumentation techniques in applied radioactivity*. Annual Progress Report, MIT 952-2, pp. 26-31. Cambridge, Mass.
- Massachusetts Institute of Technology. 1966. *Radium and mesothorium poisoning and dosimetry and instrumentation techniques in applied radioactivity*. Annual Progress Report, MIT 952-3, pp. 30-42. Cambridge, Mass.

- Massachusetts Institute of Technology. 1967. *Radium and mesothorium poisoning and dosimetry and instrumentation techniques in applied radioactivity*. Annual Progress Report, MIT 952-4, pp. 34-36. Cambridge, Mass.
- Massachusetts Institute of Technology. 1968. *Radium and mesothorium poisoning and dosimetry and instrumentation techniques in applied radioactivity*. Annual Progress Report, MIT 952-5, pp. 5-14. Cambridge, Mass.
- Mays, C. W. 1980. Personal communication. Tables prepared for occasion of Dr. Spiess's 60th birthday celebration in Munich, April 13, 1980.
- Miller, C. E. and A. J. Finkel. 1966. A re-examination of retention patterns in patients who received radium by multiple injections 33 years earlier. In *Argonne National Laboratory annual report*, ANL-7217, pp. 5-90. Argonne, Ill.: Argonne National Laboratory, Health Div., Gamma-Ray Spectroscopy Group.
- Miller, C. E. and A. J. Finkel. 1968. Radium retention in man after multiple injections. The power function re-evaluated. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* 103: 871-80.
- Miller, C. E., A. J. Finkel, and R. J. Hasterlik. 1969. *The Argonne radium studies: Computed radiobiological indices*. ANL-7680. Argonne, Ill.: Argonne National Laboratory. Also published as ACRH-107. Argonne, Ill.: Cancer Research Hospital.
- Miller, C. E., R. J. Hasterlik, and A. J. Finkel. 1969. *The Argonne radium studies: Summary of fundamental data*. ANL-7531. Argonne, Ill.: Argonne National Laboratory. Also published as ACRH-106. Argonne, Ill.: Cancer Research Hospital.
- MIT. See Massachusetts Institute of Technology.
- Müller, J. 1970. Effects of chronic irradiation and evaluation of the risk from incorporated ^{90}Sr and ^{226}Ra in man. *Acta Univ. Carol. Med. Monogr.* 45.
- Müller, W. A., W. Gössner, O. Hug, and A. Luz. 1978. Late effects after incorporation of the short-lived α -emitters ^{224}Ra and ^{227}Th in mice. *Health Phys.* 35:33-55.
- Muth, H., A. Schraub, K. Aurand, and H. J. Hanfke. 1957. Measurements of normal radium burdens. *Br. J. Radiol. Suppl.* 7:54-66.
- Norris, W. P. and H. D. Evans. 1946. *Studies on the metabolism and toxic action of injected radium*. CH-3852. Written in 1946, issued March 1948 as AECD-1965. Chicago: Manhattan Engineering District, Metallurgical Laboratory.
- Norris, W. P., T. W. Speckman, and P. F. Gustafson. 1955. Studies of the metabolism of radium in man. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* 73:785-802.
- Norris, W. P., S. A. Tyler, and A. M. Brues. 1958. Retention of radioactive bone-seekers. *Science* 128:456-62.
- Polednak, A. P., A. F. Stehney, and R. E. Rowland. 1978. Mortality among women first employed before 1930 in the U.S. radium dial-painting industry. A group ascertained from employment lists. *Am. J. Epidemiol.* 107:179-95.
- Rajewsky, B., H. Muth, H.-J. Hantke, and K. Aurand. 1957. Weitere Ergebnisse zur Frage des natürlichen Radiumgehaltes des menschlichen Körpers sowie von Nahrung und Trinkwasser. *Strahlentherapie* 104:157-68.
- Rowland, R. E. 1959. *Retention and plasma clearance of the alkaline earth elements*. Semiannual report, ANL-6104, pp. 34-47. Argonne, Ill.: Argonne National Laboratory.
- Rowland, R. E., A. T. Keane, and P. M. Failla. 1971. The appearance time of radium-induced malignancies. *Argonne National Laboratory annual report*, ANL-7860, pt. 2. Argonne, Ill.: Argonne National Laboratory, Radiological Physics Div.
- Rowland, R. E., A. F. Stehney, and H. F. Lucas, Jr. 1977. *Radium-related malignancies of female dial workers*. Presented at a World Health Scientific Group meeting held in Geneva, September 12-16, 1977.
- Rowland, R. E., P. M. Failla, A. T. Keane, and A. F. Stehney. 1971. Tumor incidence for the radium patients. *Argonne National Laboratory annual report*, ANL-7860, pt. 2. pp. 1-8. Argonne, Ill.: Argonne National Laboratory, Radiological Physics Div.
- Schäfers, F. 1978. Brief history of ^{224}Ra usage in radiotherapy and radiobiology. *Health Phys.* 35:25-32.

- Schlundt, H., H. H. Barker, and F. B. Flinn. 1929. The detection and estimation of radium and mesothorium in living persons. I. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* 21:345-54.
- Schlundt, H. and G. Failla. 1931. The detection and estimation of radium and mesothorium in living persons. III. The normal elimination of radium. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* 26:265-71.
- Schlundt H., J. T. Nerancy, and J. P. Morris. 1933. The detection and estimation of radium in living persons. IV. The retention of soluble radium salts administered intravenously. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* 30:515-22.
- Schwind, S. B. and F. E. Croxton. 1950. *Radium: A bibliography of unclassified literature.* TID-363. Oak Ridge, Tenn.: U.S. Atomic Energy Commission, Technical Information Div.
- Seil, H. A., C. H. Viol, and M. A. Gordon. 1915. The elimination of soluble radium salts taken intravenously and per os. *Radium* 5:40-44.
- Shandley, P. D. 1953. *Radium content of common foods.* Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Silberstein, H. E. 1945. *Radium poisoning: A survey of the literature dealing with the toxicity and metabolism of absorbed radium.* AECD-2122. Oak Ridge, Tenn.: U.S. Atomic Energy Commission, Technical Information Div.
- Silberstein, H. E. 1950a. Historical background. Chapter 4 in Fink 1950, pp. 157-75.
- Silberstein, H. E. 1950b. Radium distribution and excretion studies with rats. Chapter 6 in Fink 1950, pp. 179-208.
- Spiess, H. 1969. ^{224}Ra -induced tumors in children and adults. In *Delayed effects of bone-seeking radionuclides*, eds. C. W. Mays, W. S. S. Jee, R. D. Lloyd, B. J. Stover, J. H. Dougherty, and G. N. Taylor, pp. 227-47. Salt Lake City: Univ. of Utah Press.
- Spiess, H. 1978. Clinical experiences concerning late effects and risks of ^{224}Ra . In *Biological effects of ^{224}Ra* , eds. W. Muller and N. G. Ebert, pp. 102-8. The Hague: Martinus Nijhoff.
- Spiess, H., A. Gerspach, and C. W. Mays. 1978. Soft-tissue effects following ^{224}Ra injections into humans. *Health Phys.* 35:61-81.
- Spiess, H. and C. W. Mays. 1970. Bone cancers induced by ^{224}Ra (Th X) in children and adults. *Health Phys.* 19:713-29.
- Spiess, H. and C. W. Mays. 1973. Protraction effect on bone-sarcoma induction of ^{224}Ra in children and adults. In *Radionuclide carcinogenesis*, eds. C. L. Sanders, R. H. Busch, J. E. Ballou, and D. D. Mahlum, CONF-720505, pp. 437-50. Proceedings of the 12th annual Hanford life sciences symposium held in Richland, Wash., May 10-12, 1972. Springfield, Va.: National Technical Information Service.
- Spiess, H. and C. W. Mays. 1979. Liver diseases in patients injected with ^{224}Ra . *Environ. Res.* 18:55-60.
- Stannard, J. N. 1973. Toxicology of radionuclides. *Annu. Rev. Pharmacol.* 13:325-57.
- Stannard, J. N., H. A. Blair, and R. C. Baxter. 1964. Mortality, life span, and growth of rats with a maintained body burden of polonium. *Radiat. Res. Suppl.* 5:228-45.
- Stehney, A. F. and H. F. Lucas, Jr. 1956. Studies on the radium content of humans arising from the natural radium of their environment. In *Proceedings of the international conference on the peaceful uses of atomic energy*, vol. 11, pp. 49-54. Held in Geneva, August 8-20, 1955. New York: United Nations.
- Stehney, A. F., H. F. Lucas, Jr., and R. E. Rowland. 1978. Survival times of women radium dial workers first exposed before 1930. In *Late biological effects of ionizing radiation*, STI/PUB/489, vol. 1, pp. 333-51. Proceedings of a symposium held in Vienna, March 13-17, 1978. Vienna: International Atomic Energy Agency.
- Taylor, G. N., T. F. Dougherty, L. Shabestari, and J. H. Dougherty. 1969. Soft-tissue tumors in internally irradiated beagles. In *Delayed effects of bone-seeking radionuclides*, eds. C. W. Mays, W. S. S. Jee, R. D. Lloyd, B. J. Stover, J. H. Dougherty, and G. N. Taylor, pp. 323-36. Salt Lake City: Univ. of Utah Press.
- Thomas, H. E. and F. H. Bruner. 1933. Chronic radium poisoning in rats. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* 29:641-62.

United Nations Scientific Committee on the Effects of Atomic Radiation. 1977. *Sources and effects of ionizing radiation*. 1977 Report to the General Assembly. New York: United Nations.

UNSCEAR. See United Nations Scientific Committee on the Effects of Atomic Radiation.

Weikel, J. and E. Lorenz. 1947. *Excretion of radium from the mouse*. MDDC-1587. Argonne, Ill.: Argonne National Laboratory.

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Capsule Chronology

- 1824** Uranium described in Gmelin's Handbook.
Much animal toxicity work done thereafter.
- 1860** Uranium first used in homeopathic medicine for treatment of diabetes. There follow over fifty years of clinical use. Animal toxicology work parallels the clinical uses. Much effort expended on trying to use uranium in animals as model for kidney changes caused by nephritis in man—largely unsuccessful.
- 1895** Rutherford shows that "uranium emanation" has the spectral line of helium.
- 1896** Becquerel demonstrates the radioactivity of uranium.
- 1904** Rutherford shows that alpha particles are helium atoms and works out the natural decay series.
- Next three decades** Sporadic work on toxic effects in cells. Much work on effects on blood chemistry, various physiological systems and organs, histological changes, repair processes. Tolerance demonstrated in 1920s.

WORLD WAR II

- 1942** Realization that enormous quantities of uranium would have to be handled in the Manhattan Engineer District work. Tracer work at Berkeley (Hamilton).
- Late 1942** Beginning of biomedical work in Chicago at Michael Reese Hospital and later the Metallurgical Laboratory (Tannenbaum, Singer, Barron, and colleagues). Effects on cells as well as whole organisms.
- 1943** Organization of extensive program at University of Rochester, which emphasizes acute toxicology at the start but also goes deeply into biochemical mechanisms, complexing, and an extensive program of inhalation toxicology, which is detailed in chapter 9. All varieties of uranium compounds, several species of animals, and all types of effects are studied. (Hodge, Neuman, Rothstein, Voegtlin, Maynard, Stokinger, Dounce, and scores of colleagues).
- 1942-1947** Attempts to devise sensitive tests for kidney damage in man. Determined that only a battery of tests is reliable.
- Late 1940s** Work at Chicago on higher-specific-activity isotopes of uranium begins. Reported postwar.
- 1948** Six patients at University of Rochester who received uranium for kidney function tests described (injections done earlier in the war). Threshold for kidney damage described.

POST-WORLD WAR II

- 1949 and 1953** Rochester work with uranium done during war years published in four-volume set under National Nuclear Energy Series (Voegtlin and Hodge).
- 1951** Chicago work on uranium published as volume in National Nuclear Energy Series (Tannenbaum).

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- 1951 et seq. Eleven-year chronic inhalation experiment begins at Rochester in 1955. Five years of exposure, six years of postexposure observation and measurement. Pulmonary lymph nodes are necrotic and full of uranium. Lung damage similar to that seen with plutonium. At longest times and highest doses lung cancer demonstrated in dogs but not monkeys.
- 1949 et seq. M. Finkel, at Argonne National Laboratory, follows up on relative effectiveness of ^{233}U compared to ^{226}Ra in mice. Publications in 1950s et seq.
- 1950s Animal studies at Oak Ridge on uranium compounds of most concern in their operations.
- 1950s Cooperative study of eight patients between Massachusetts General Hospital-Boston Veterans Administration Hospital and Oak Ridge National Laboratory. Mid-1950s: metabolism found similar to animal studies.
- 1955 Oral administration of uranium to man by Butterworth, 1955, with marked effects; by Hursh et al. 1969, with lower dose and no measurable effects. Metabolism found similar to that in animals.
- 1950-1970 Depositions in tissues from industrial exposures checked by bioassay of excreta and whole-body counting, also from autopsy material. Amounts of uranium in lung of man far lower than predicted from metabolic data and air sampling results.
- 1950 et seq. Evidence for kidney damage in industrial exposures much less than anticipated. Leads to postulate that man is significantly less sensitive to toxic effects of uranium than experimental animals. First discussed at New York symposium in 1958; expanded at Arlington symposium in 1975.
- 1973 Key reviews by Hursh and Spoor, Spoor and Hursh.
- 1978 Uranium Registry finally established.
- Late 1970s-1980s Bona fide epidemiologic study of Tennessee Eastman plant workers exposed during World War II now in progress (late 1970s and early 1980s). Utilizes personnel data obtained during war and current or recent past determinations of effects.

Chapter 2

Uranium

Overview

This chapter reviews the highlights of a research effort referred to near its completion as "the most comprehensive experimental investigation of an industrial poison ever carried out . . . in such a short time" (Voegtlin and Hodge 1949). Probably a greater effort has now been expended on plutonium, but the time span is quite different.

Much "basic science" that came out of the uranium work can only be alluded to in this chapter. Also, several major aspects, which involved primarily inhalation toxicology, are reserved for the large section on that topic (chapter 9). Conversely, one of the largest and longest inhalation experiments is taken up here because it provides a fitting extension of the work done in the fever heat of the war effort.

This chapter is unique in that much of the concern is with chemical toxicity rather than radiation effects. From time to time, other long-lived radioelements have been regarded as carrying a component of chemical toxicity along with radiation effects. Plutonium was so regarded in the early days, and there is still some residual musing on the idea. Thorium in Thorotrast is another candidate. But neither these nor others suggested have demonstrated the clear-cut chemical (nephrotoxic) action of ^{238}U and natural uranium. Yet, there is a radiation component in uranium toxicity if enough time is allowed or if mixtures enriched with the shorter half-life uranium isotopes are used.

To conserve space, this chapter must leave out many interesting and worthy contributions, but it is hoped the presentation has captured the flavor of the research as well as its fervor and will show how concentrated work on practical goals can still provide valuable insights into chemical and biological mechanisms, some of which have grown into now discrete and sophisticated fields of inquiry. Some of our contemporary problems with nonradioactive substances deserve an attack similar to that organized around uranium, but the will and the organization seem to be lacking.

I. Introduction

The research with uranium, both natural and the shorter-lived more radioactive isotopes, was primarily directed toward the prevention of occupational over-exposure. Some of the dirtiest operations in the Atomic Bomb Project were in the handling of uranium ore and the several uranium salts prepared in the passage from ore to nuclear fuel. In one step, the production of "green salt," at least one worker became so immersed in his work that he was known as "The Green Hornet" after a popular cartoon character of the day. (Fortunately absorption was minimal.)

These conditions were not in callous disregard of the health of the workers but because of the pressures of the war to do things in a hurry. A major effort was mounted in uranium toxicology, primarily natural uranium. The results were applied to industry as quickly as they could be, and in general, it appears, in time to prevent a major long-term disaster for the hundreds of workers involved.

This chapter concerns this research. Applications to inhalation problems, except for one chronic exposure experiment, and to standards are deferred to chapters 9 and 16, respectively. Environmental contamination problems with uranium are considered in chapter 11.

It has been customary to state that little was known about the biological effects of uranium when the decisions were made to develop the atomic bomb; organize the Manhattan Engineer District (MED); and proceed to mine, handle, and store quantities of uranium orders of magnitude greater than ever before. Actually, a great deal of work had been done. Hodge (1973), in his monumental compendium, "A History of Uranium Poisoning (1824-1942)," has over four hundred references in the bibliography. This author has close to two hundred cards on work before 1942 accumulated without any special effort to reach into the early history. Uranium was used empirically in medicine, and its acute effects on the kidney were fully appreciated in the late nineteenth century. In fact, uranium was used widely in experimental medicine to induce in animals a nephritis that it was hoped would duplicate the disorder seen in man. In addition, there is a large literature on the effects of uranium on lower organisms. There was also some crude information on its acute toxicity in higher organisms by the time the MED began.

Why then was it felt necessary to mount a major effort on uranium toxicology at the beginning of the MED effort? First, it was known that uranium was toxic, but there was essentially no information on what levels might be innocuous or "tolerated." Second, the route of entry was most likely to be inhalation. Almost all of the earlier work involved parenteral administration. Third, many new compounds were expected to be involved. Fourth, the number of potential exposed individuals was legion compared to any previous operations, and the expected quantities were enormous. For these reasons, and perhaps because of the knowledge that uranium was potentially very toxic, a major effort was decided upon. I suspect the characterization "the most comprehensive experimental investigation of an industrial poison ever carried out by any group of scientific workers in such a short time" (Voegtlin and Hodge 1949) could well embrace all of toxicology, not just industrial poisons.

As indicated in the overview, the work on uranium differs markedly in outlook from that surrounding any other element or group in this compendium. Natural uranium is so weakly radioactive that its potential as a chemical poison far outweighs any possible radiation hazards, at least in terms of acute toxicity.

A true threshold below which no effect would occur was expected for uranium, as for most chemical poisons then known. Also, the usual sigmoid dose-response curve was assumed to hold (and was found). The only exceptions to the lack of radiation effect were the possible effects of the higher-specific-activity isotopes and uranium fuel enriched with these, and the possibility that long-term exposures to insoluble compounds, even of natural uranium, might, given long enough, pose a radiation hazard.

II. World War II

A. General Organization

The laboratory studies of uranium began almost immediately after the organization of the Medical Section of the Manhattan Project. They were so extensive and so intensive that they might be compared to a major military operation—a sort of “storming of the heights.” Two laboratories undertook the bulk of the work: the Project at the University of Rochester Medical School, Rochester, New York.

At Rochester, the work began by sealing off with guards a portion of the biochemistry department in the basic science section of the school, as well as constructing a “temporary” building across the street from the Medical Center attached to a building housing one of the early million-volt x-ray machines. Within a year, this building was extended with a one-story addition, which was deceiving in size. These facilities were able to house not only the laboratory work but a very sizeable animal facility for the development of the Rochester strain of the Wistar white rat. (Holding facilities for larger animals were in the earlier building.) Pictures of this facility as it was in World War II and as it now looks are shown in figures 2.1 and 2.2.

It is difficult to imagine that as many as 350 workers operated in that facility. While not all were devoted to the uranium work, as later chapters will describe, that effort was the largest single enterprise.

Dr. Harold C. Hodge directed the undertaking at Rochester with senior assistants brought in from the most disparate of backgrounds. (Their names will appear as we proceed in this and chapter 9.) Of course, tight security was clamped upon the operation, and the process of compartmentalization began as described by others dealing with the general history of the Manhattan Engineer District (e.g., Friedell 1981). Since the project was geographically closely integrated with the school, the imposition of security measures led to some friction, which was augmented by the fact that the pay-scale in the project was higher than in the rest of the school. There is a story (Neuman 1978) that the dean of the medical school^(a) decided one day to see what was going on in what was still part of his biochemistry department. Although he undoubtedly later on had full security clearance, he did not have the proper papers for entrance, and the guard refused to let him in. It is stated that the dean never again set foot in the project until after the war years.

The approach was very much a mass production format. There were working groups for hematology, pathology, and so forth of considerable size (figure 2.3). Work went on a three-shift basis, with individual workers in each group receiving material with only code numbers.

(a) Dr. George H. Whipple, Nobel Prize winner for his work on anemia.



FIGURE 2.1. Early view of the "temporary" buildings housing the MED work at the University of Rochester Medical Center. The one-story building at the right included the animal colony and most of the inhalation exposure chambers. Note that as many as 350 people worked in this facility, about half of them on the uranium work, on eight-hour shifts around the clock. (Courtesy of University of Rochester Medical Center Photographic Unit.)



FIGURE 2.2. Later picture of the University of Rochester facility that housed, in part, the Post-World-War-II uranium studies. A third story had been added to the central section. (Courtesy of University of Rochester Medical Center Photographic Unit.)



FIGURE 2.3. Group picture of Hematology Group, which worked largely on the MED uranium experiments at the University of Rochester. (Courtesy of the University of Rochester Medical Center Photographic Unit.)

The work at Chicago began at the Medical Research Institute of Michael Reese Hospital and was concentrated there, although some went later to Site "B," a former brewery fitted up for laboratory research. An outside view of this handsome facility is shown in figure 2.4. It was part of the Metallurgical Laboratory of the Manhattan Project and was really a side-show of the Plutonium Project. The work on uranium was under the direction of Albert Tannenbaum with special assistance from Samuel Schwartz and others listed in the references for this chapter. It was under the broad supervision of Robert S. Stone, Chief of the Health Section of the Metallurgical Laboratory.^(a)

Since the Chicago project was taken up with plutonium, fission products, and other important aspects of the broad effort, the uranium work was not as intensive or extensive as it was at Rochester. But it was a very significant contribution. It was concerned largely with injection and ingestion and with mechanisms, a fundamental area where it was well to have two laboratories at work. There were a few isolated studies elsewhere.

In addition to the intensive laboratory work, there was of course the need for industrial and field measurements and interpretations. The industrial control aspects will be considered in a separate section, and the complicated and very significant problems of uranium mining are taken up in chapter 3.

(a) The work at Michael Reese Hospital seems to have preceded by a few months that at Rochester, and Tannenbaum remained there almost exclusively. But the very earliest MED work on uranium, like so much else we will discuss in later chapters, seems to have involved tracer studies, in this case with ^{233}U , in the Berkeley laboratory of Joseph G. Hamilton (Hamilton 1948a,b,c).



FIGURE 2.4. An outside view of "Site B" of the Metallurgical Laboratory at Chicago. This was the delivery alley. The converted brewery held most of the animal work on fission products and transuranics and some of the uranium work. Most of the uranium work was done at the Michael Reese Hospital. No pictures were allowed of the inside of Site B because of security regulations. (Courtesy of Drs. Austin Brues and Miriam Finkel.)

B. The Initial Approach to the Toxicology

Despite the large amount of work with uranium already done, none of it really addressed the immediate needs of the Manhattan Project. What toxicological information was available involved levels far too high to guide even these early wartime efforts. As Hodge vividly describes in the foreword to the first volume accounting the war work in the National Nuclear Energy Series (NNES) (Voegtlin and Hodge 1949), the need was to know levels that would be without *serious sequelae*. Which of the numerous uranium compounds were more dangerous, and exactly how toxic was each? This meant initial experiments at levels that would produce effects in reasonably short periods followed by work at lower and lower levels and longer and longer exposure periods. It also meant the development of much more sensitive methods for measurement of low concentrations of natural uranium. It meant development of reasonably quantitative methods for inhalation exposure, and, if possible, some reliable and simple tests for damage produced by any exposure.

Some of the very early instrumentation and methodology were unbelievably crude by the standards of even a few years later. Dr. William F. Neuman at Rochester described to this author (Neuman 1978) how his assignment to develop an ultramicro analytical method for uranium got under way. Dr. Walter Bloor, who was chairman of the biochemistry department of the medical school and an analytical chemist, used an old colorimeter to fashion a spectrophotometer whose light path was conditioned by passing it through some amber glass

from broken beer bottles. The source was a headlamp from a Model T Ford operated from a six-volt storage battery. The receiver was a plain photocell connected to a wall galvanometer with a light path of about 35 ft.^(a) Yet, this was the beginning of a truly ultramicro method (see "The Fluorophotometric Determination of Uranium" by Bloor and Neuman 1949 and Neuman et al. 1948a).^(b)

Similar crude beginnings for the early inhalation studies are described by Rothstein (1978). There was little time for formality. The investigator, a carpenter, and a machinist might get together, discuss a general layout, and go ahead to build the needed equipment by trial and error. A useful exposure chamber unit was thus constructed, even though the first "dust feed" consisted of a large salt shaker being banged against a heavy metal base plate!

Despite the compartmentalization of thought and effort imposed by security restrictions, it appears that the Chicago and Rochester groups had enough high-level conferences to make decisions on the broad scope of each laboratory's work. It is not so clear how much information was exchanged on methodology. Since Chicago was to do only ingestion and injection for toxicology investigations, they were spared the onerous task of building inhalation exposure chambers and dust feeds. But they did need to measure uranium. Reference to methodology on uranium is scarce in the early MED literature from Chicago. But we do find citation of "Fluorophotometric Determination of Uranium" (Price, Ferretti, and Schwartz 1953) in one of the oldest of the report series. Whether this was developed independently of the Rochester effort is not clear; at least the same principles seem to have been utilized.

While these experimental studies were getting under way it was necessary to establish working rules for the workers already beginning the processing of uranium ores, and beginning operation of the many chemical steps of separation, and the fabrication of fuel elements. Since lead had been studied extensively and there was much experience both in animals and in exposed workers and members of the general population, and there were many apparent similarities between uranium and lead, an interim daily exposure level for uranium was devised by analogy to lead. This took care of the immediate industrial exposure criteria, and the laboratory work could get under way in earnest in parallel with the early process development.

C. The Initial Toxicology Results

The results of the uranium work on animals at Rochester and at Chicago have been documented in extenso in the volumes of the NNES (Voegtlin and Hodge

- (a) The wavering path of the galvanometer light spot in a building constructed on piles over quicksand and the agonizing slowness of this procedure are factors only those who have had to use such methods can appreciate.
- (b) As was the custom throughout the Manhattan Project, several methods were developed simultaneously since there was no time to wait for sequential developments. The result was frequently a variety of methods used for different levels of sensitivity, convenience, etc. The sensitivity of the fluorophotometric method was astonishing for a chemical (as contrasted to a radiochemical) method. The Chicago group gave their sensitivity as 0.001 μgm uranium (Ferretti and Schwartz 1946); the Rochester group gave 0.005 γ/g (Neuman et al. 1948a). Obviously, the car headlamp had been replaced by an ultraviolet light source, and many other changes were made before the fluorophotometric method achieved the sensitivity just given.

1949; Voegtlin and Hodge 1953; Tannenbaum 1951), in summary fashion by Yuile (1973), and by Durbin and Wrenn (1975).^(a)

The initial work involved primarily the rat at Rochester and the mouse at Chicago, but other species entered as the work progressed. Every conceivable route of entry was tried: parenteral injection (i.e., intravenous or intraperitoneal), feeding, application to the skin and to the eye, and inhalation. The first experiments were short-term, e.g., twenty-four-hour mortality, mortality in fourteen to twenty-one days, etc. But these were soon extended to thirty-day feeding tests involving dogs and rats, one-year feeding tests with dogs and rats, and inhalation exposures from acute ("pilot tests") to repeated exposures for up to one year.

The compounds studied were legion and included the gas uranyl hexafluoride (UF_6), UO_2F_2 , uranyl nitrate, UCl_4 , UF_4 , "high grade ore," UO_2 , UO_3 , UO_4 , $\text{Na}_2\text{U}_2\text{O}_7$, $(\text{NH}_4)_2\text{U}_2\text{O}_7$, and U_3O_8 . The highlights of the earlier toxicological findings are summarized below.^(b)

1. There is a wide range of transportability of the various uranium compounds. Perhaps the easiest way to illustrate this is to borrow a table (table 2.1) prepared by Scott (1973) and published in the volume edited by Hodge, Stannard, and Hursh (1973).

TABLE 2.1. Classification of Uranium Compounds According to Transportability^a

Highly Transportable	Moderately Transportable	Slightly Transportable
UF_6	UO_2^b	UO_2^b
UO_3^b	U_3O_8^b	U_3O_8^b
$\text{UO}_2(\text{NO}_3)_2$	UO_3^b	Uranium oxides
UF_4^b	UF_4^b	Uranium hydrides
Uranium sulfates	Uranium nitrates	Uranium carbides
Uranium carbonates		Salvage ash

^a Partially developed from data by Steckel and West (1966), and Task Group on Lung Dynamics (1966).

^b Subjecting a particular uranium compound to higher temperatures tends to decrease rate of transportability.

Source: Reset from Scott 1973; references included in the bibliography for this chapter. Reprinted with permission of Springer-Verlag, Heidelberg, copyright 1973.

(a) The reviews of Yuile and of Durbin and Wrenn include both the MED days and post-war work. The discussion by Durbin and Wrenn includes consideration also of unsolved problems and is very complete and authoritative. For the original data, the series of papers by Neuman and colleagues in 1948 and 1949, and the Voegtlin and Hodge volumes should be consulted.

(b) Although the citations are postwar, the basic phenomena described in this section were apparent in the war work, with some obvious exceptions.

2. The "soluble," i.e., transportable forms of natural uranium are deposited primarily in kidney and bone.^(a) They leave the kidney quickly and are excreted largely via urine. If the levels are above the threshold for kidney damage, effects localized almost entirely to the proximal convoluted tubule can result. Only at very high levels does the damage extend to other parts of the kidney. The glomerulus seems singularly immune under ordinary circumstances.
3. Recovery from kidney damage, unless severe, is relatively complete. The cells replacing the damaged epithelial cells are different from those damaged by the uranium and are much less sensitive to subsequent exposures to uranium. This leads to the well-documented phenomenon of development of tolerance to uranium.
4. The insoluble forms tend to remain at the site of entry. Since this is usually the lung, large deposits of compounds such as uranium dioxide can accumulate in lung and accessory structures.
5. Biochemical changes occur concomitantly. These will be considered in a separate section.
6. Bone retention is long relative to retention in soft tissues, and uranium seems to enter bone by partial exchange^(b) for calcium and enters loosely into the hydroxyapatite crystal (Neuman and Neuman 1958). It does not seek bone surfaces as do plutonium and the actinide elements. (Also, as later work showed, it does not penetrate the crystal lattice of hydroxyapatite. It remains only at the crystal surface in contrast to calcium and related small ions. See Durbin 1986.)
7. Soluble uranium compounds can pass through the skin and can enter the body through the eye if splashed thereon.
8. Differences in species susceptibility are large but are so variable among the compounds that no generalizations can be made. Nevertheless, Hodge developed a composite score for toxicity (Voegtlin and Hodge 1949), which is reproduced as figure 2.5.
9. Significant increases in sensitivity of the analytical methods were accomplished, even though by current standards the equipment itself would seem crude.

D. Biochemical Aspects

The people recruited for the more senior posts in the toxicology effort were far from technical hacks, as was sometimes implied. They were good scientists, and, as good scientists, they instinctively turned attention to mechanisms and explanations whenever the opportunity presented itself. Fortunately, those in the higher medical echelons of the MED knew that the more there was known about mechanisms the more chance there was for intelligent treatment and control. They did nothing overt to discourage these investigations so long as

(a) Despite the mass of pre-World-War-II work on uranium, standard pharmacology texts never mentioned the deposition of uranium in bone, only its deposition in and effects on kidney.

(b) In the earlier literature, a full ion exchange process between uranium and calcium was considered proven. Since it appeared later that the uranyl ions did not penetrate fully into the hydroxyapatite crystal, I have termed the process *partial exchange*.

TOXIC RESPONSE SCORE	DUST	LEVEL mg/U/M ³
4	UF ₆	13
5	UO ₂ F ₂ ; UCl ₄	>9, 11
5.5	UO ₂ (NO ₃) ₂	11
6.5	UO ₄	13
7	UO ₃	16
8	"HI-GRADE" ORE	20
9	Na ₂ U ₂ O ₇ ; UF ₄	15, 18
9.5	(NH ₄) ₂ U ₂ O ₇	12
11	UO ₂	19
15	U ₃ O ₈ *	15
16		

*The position of U₃O₈ is fixed with less certainty than the others because of less detailed study.

FIGURE 2.5. Relative toxicity of twelve uranium dusts on a scale of four to sixteen. The route of entrance was inhalation. (Redrawn from Voegtlin and Hodge 1949, p. 40.)

sight of the primary practical goal was not lost, even though they could not openly condone or encourage any deviation from the mission-oriented approach.^(a)

The chemistry of uranium and its compounds was worked out exhaustively in the MED years as well as later. A good idea of the depth and breadth of the chemical information developed can be seen in the postwar review by Gindler (1973). Against this background, much could have been done more quickly in the MED days. However, the biomedical workers had to find out for themselves, since most of the chemistry described later was in a classified status during the war.

1. Complexing

The known chemistry of uranium had already pointed to its strong tendency to form anionic complexes with many moieties. In the early results of the MED, it was determined that the most important of these were complexes with protein

(a) This is a generalization. There were instances of open conflict between the higher military echelons and the MED scientists, and a certain amount of mutual contempt developed. This drove the mechanistic work underground to a degree. The portion of the budget allowed to be devoted to nonprogrammatic work was only 20% in the second year (none specifically allocated in the first year) and only gradually increased to allow 50% for mechanistic work in later years.

and with bicarbonate. Complexing with protein was considered the basis for the toxic action of uranium in the kidney, i.e., combination with the protein of the cells lining the tubular epithelium. The complex with bicarbonate was critical, because a significant portion of the uranium in blood was complexed with bicarbonate and entered the kidney tubules as such. In the proximal convoluted tubule, the urine becomes more acid, and the complex with bicarbonate is dissociated, leaving the uranyl ion free to attach to protein of the tubular epithelial cells. In this way, a reasonable explanation for the relative anatomical localization of uranium damage in the kidney was possible.

Many of the workers both at Chicago and Rochester were sophisticated chemists. The complexing process and systems receive detailed treatment in the chapters by Neuman and Tishkoff (1953) and in less detail in one by Barron (1951). Regardless of direct application or lack of it to biologically prime processes, the solution chemistry of uranium received ample and sophisticated study. The results have been and will remain valid for a long time.

One simple conclusion is that normally uranium is carried in the +6 valence state when in solution in biological fluids.

2. Urinary Tests for Kidney Damage

Long before the MED work began, it was known that animals or humans with kidney damage excreted protein (albumin) in the urine. Later it was clear that certain enzymes, such as acid phosphatase, also appeared in urine.

Considerable effort was expended to find a really sensitive, and preferably easy-to-determine, excretory product that might signal the onset of kidney damage in uranium workers. The most promising among these was the excretion of the enzyme catalase in the urine. This was developed in detail at Rochester (Dounce, Roberts, and Wills 1949) and also at Chicago (Katz, Holt, and Schwartz 1946). It came apparently from the damaged cells of the tubules by either a change in permeability or cell breakdown and was in no way correlated with glomerular filtration rate. It was more specific than proteinuria, and the catalase activity of urine was easily determined.

All of the animal experiments pointed to the excretion of catalase as a very promising measure of threshold kidney damage. It was, therefore, a considerable disappointment when it was found and reported by the Chicago group that it did not work in man (Katz, Holt, and Schwartz 1946) at levels of uranium exposure anticipated in practice. Personnel from the Ames Research Laboratory (Iowa State University) showed no significant difference among twenty-six individuals chronically exposed to fairly large amounts of uranium and twenty-three control students. Nor was there any elevation of urinary catalase in Project personnel exposed to smaller amounts (Schwartz 1951a, p. 38; also Katz, Holt, and Schwartz 1946). It should be added, however, that from what we now know of the actual amounts of uranium entering the body in cases originally set down as "fairly large exposures," the problem may have been more one of underexposure than lack of sensitivity of the test in man. (These problems will be reviewed further in chapters 9 and 16.) Many other entities appear in the urine of animals exposed to uranium. These include coproporphyrin, various enzymes, protein, amino acids, etc. But none seemed to be really specific, and monitoring of man seems to have settled on albumin and cell debris, even though it appears that a careful monitoring of amino-acid excretion is really the best indicator (Rothstein 1978) or possibly a combination of three tests (Hodge 1953a in Voegtlin and Hodge 1953, p. 2391).

3. Metabolic and Cellular Effects

It was established early that uranium was a potent enzyme inhibitor. In the Chicago work, Barron (1951) at first assumed the effects were by inhibition of sulfhydryl enzymes—Barron was a strong proponent of this very popular notion for a large variety of drugs and toxic agents (Barron, Muntz, and Gasvoda 1948). The Rochester group could find no evidence that this was the mechanism (Dounce 1949). Despite the barrier of security, a moderately heated polemic ensued. But by the time the more complete papers were written (e.g., Singer et al. 1947) there was no contest. Indeed the evidence presented—no loss of -SH titer, lack of reversal by BAL (British anti-lewisite) or glutathione, and lack of correlation between sensitivity to UO_2^{++} and the presence of “essential” SH groups—eliminated any possibility that enzyme inhibition by uranium involved sulfhydryl group combination. The physical-chemical work at Rochester was pointing to quite a different mechanism anyway. Other metabolic studies were summarized by Berke et al. (1953).

Unfortunately, despite a very considerable amount of work, no close association between specific enzyme inhibition as measured in vitro and uranium's toxic effects could be drawn (Dounce and Lan 1949). However, a very exciting prospect developed out of work at both Rochester and Chicago using intact cells. This was followed up insofar as was feasible even during the war years. It led to an entirely new view of the functions of the cell membrane and formed the basis for several productive postwar scientific careers, indeed for the entire field of membrane biophysics.

Briefly, the story begins with the finding of extraordinary sensitivity to uranyl ion of glucose uptake by intact yeast cells (Muntz, Singer, and Barron 1947).^(a) Concentrations as low as 10^{-5} M of uranyl ion had marked effects. This was readily reversed by the addition of phosphate to the medium. Rothstein (1953) and his colleagues followed through with very detailed studies that proved that the action on intact cells was quite different from that in a maceration juice. (The Chicago group also demonstrated this.) *The uranyl ion did not pass through the cell membrane.* Thus, the uranium was complexing with entities in the cell surface, i.e., active groups of enzymes. It was exerting most of its effect on glucose uptake without even entering the interior of the cell! Thus, for the first time, the presence of enzymatic reactions vital to cell metabolism was demonstrated to reside in the cell surface or membrane. The details and ramifications of this work, begun as part of the MED practical work, came to full flower in the postwar years (more in chapter 21).

It remains somewhat an open question as to the extent to which these cell surface reactions account for the action of uranyl ion in the kidney tubule, but the importance of the findings to cell biology stands regardless.

Whole-animal biochemistry, i.e., clinical chemistry, was investigated in most of the studies. The results, described in the NNES monographs already cited, indicate that systemic uranium can interfere with normal carbohydrate metabolism of dogs and rats (Hodge 1953b). If enough uranium is given, organs other than kidney (e.g., liver) begin to show alterations of metabolism. Some alterations in porphyrin metabolism, not incontrovertibly associated with a direct action of uranium, turned up in the Chicago work (Schwartz 1951b). Most of the changes in clinical biochemistry could be referred to kidney lesions and disorders of kidney function at doses near the threshold level.

(a) A large variety of cell systems was studied in addition to yeast, but cannot be detailed here.

4. Bone

Uranium deposits primarily in kidney and bone. It leaves kidney and other soft tissues very rapidly. Thus, deposition in bone is the most important long-term storage mechanism for uranium introduced in soluble form. The detailed biochemistry of the processes involved, as studied during the MED days, is summarized by Neuman in many papers in the open literature and most easily studied in his chapter in the Voegtlin and Hodge monograph (Neuman 1953). The fact that it enters largely by ionic exchange processes and is a "volume seeker" in modern parlance was amply clear.

In addition to studies on whole animals to determine the role of factors such as age, diet, etc., a large effort went into in-vitro studies. These have become an integral part of today's background for the biochemistry of the heavy metals and cations in general in bone (Neuman and Neuman 1948, 1958; Neuman, Neuman, and Mulryan 1948; Neuman et al. 1948b; 1949a,b,c).

Somewhat akin to the work on cell surface enzymes, this wartime work on bone formed the basis for some other postwar careers and fields of activity.^(a)

Perhaps because of the weak radioactivity of natural uranium, perhaps because of the biochemical interests of most of the investigators, the possibility that uranium deposited in bone might be a source of cancer is never mentioned in the literature of those days. This stands in sharp contrast to the attention directed to carcinogenesis from the more highly radioactive bone seekers such as radium, plutonium, strontium, etc. There is no evidence that natural uranium has ever produced a bone tumor; nevertheless, the difference in viewpoint is interesting. It may well reflect the compartmentalization engendered by security as well as the different interests of the investigators.

E. Pathology

The gross and microscopic pathology of uranium poisoning was already well understood at the beginning of the MED days. Naturally, routine histopathology was done in most of the toxicity experiments, but the results served largely to "fine-tune" what was already known.

Perhaps the most efficient way to summarize is by quoting from Yuile's (1973) description of the animal studies:

Since the earliest animal experiments with uranium, there have been numerous descriptions of the morphological expression of its renal toxicity based on experiments on animals of various species, age and sex. Different uranium compounds have been given in widely different doses and by various routes as either single or repeated administrations. Despite these differences, remarkable similarities are noted between the numerous pathological descriptions and interpretations found in the literature. The changes, which share many features with poisoning by other heavy metals such as mercury, are not specifically diagnostic of the effect of uranium. There is, in general, an inverse relationship between the time of onset and severity of the renal lesions and dose in any given susceptible species.

The proximal convoluted tubules show the earliest change consisting of vacuolization and the accumulation of hyalin droplets and other cytoplasmic bodies. There is a lag period of from about 6 hours to several days in the appearance of these changes, depending on the dose, and ultimately, with administration of

(a) In combination with work on the radioactive alkali metals and the actinides, much of modern bone physiology and biochemistry got its start in these MED studies.

sufficient amounts of the material, cell necrosis is seen. The necrosis appears initially in the lower portion of the convoluted tubule. With lower doses it is spotty in distribution and following higher doses, may extend as wedge-shaped areas into the outer cortex toward the capsule. Casts, either hyalin or containing shed necrotic cells, are present in considerable numbers after the first few days at all levels of the tubular system. After 2 or 3 days, evidence of regeneration of the lining of the convoluted tubules becomes apparent, depending, to some extent, on the severity of the initial injury. In non-fatal cases, after about 2 to 3 weeks, the lining epithelium is completely reformed but the individual cells are morphologically and functionally abnormal for considerably longer periods of time. Regenerating epithelium takes several forms. Nuclei tend to be larger and darker than normal, with mitotic figures being frequently seen in the early stages. Cytoplasm is basophilic and often flattened. As regeneration continues and the kidney becomes more and more normal in appearance following sublethal doses of uranium compounds, subtle changes are seen for a considerable period of time so that it is difficult to distinguish between regenerated cells and cells which have been "activated" in some fashion. (Yuile 1973, pp. 186-187)

III. Postwar Animal Studies

At the conclusion of World War II and the disbanding of the Manhattan District, many projects were in midstream and required much more work to realize a return on the investment of the MED efforts. This was not true for natural uranium. The prodigious efforts of the war years could be regarded as having accomplished most of their goals. The chief residual problems concerned the metabolism and possible radiation effects associated with very long-term exposure to insoluble uranium compounds, some miscellaneous extensions on specific problems, and the acquisition of more and better data on man. This section takes up the postwar animal studies with direct connections to the earlier work.

A. The Rochester Inhalation Experiment

By far the most extensive postwar experiment with animals was a long-term inhalation project at Rochester. The purpose was both the determination of retention and "metabolism" and potential development of long-term effects in the lung and accessory respiratory structures. By using insoluble UO_2 dust, the potential for chemical effects on the kidney was minimized. An entirely new exposure chamber set-up was designed and built. A picture of the installation is given in figure 2.6. Exposure started in 1955 under the auspices of the University of Rochester Atomic Energy Project, supported by the Atomic Energy Commission (AEC). Rats, monkeys, and dogs were exposed for six hours per day, five days per week to an aerosol containing about 5 mg/m^3 with mass median diameter of about $1 \mu\text{m}$ for a maximum period of five years in the dogs and monkeys. There were serial sacrifices to determine distribution and retention and clinical determination of the general health of the animals. Despite the accumulation of large quantities of UO_2 dust in lung and tracheobronchial lymph nodes, there was little transfer to kidney or other tissues and no evidence of kidney damage or hematologic changes. The results to the end of the five-year exposure period were described by Leach et al. (1970). Except for fibrotic changes in the lymph nodes of monkeys and dogs suggestive of radiation injury and some lung changes in monkeys, there was surprisingly little obvious effect in the five years of exposure.

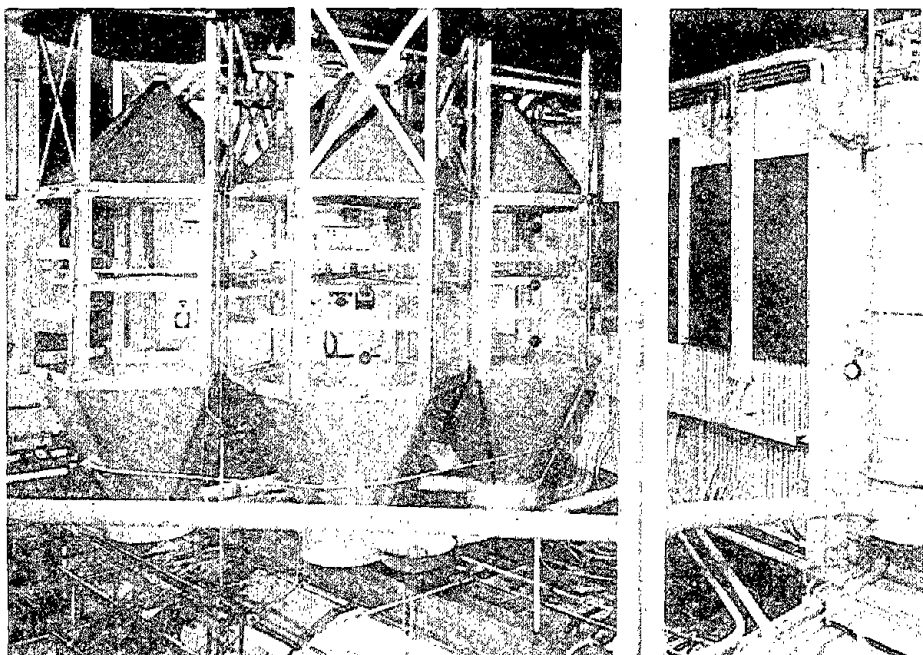


FIGURE 2.6. Photograph of one bank of the inhalation chambers used for the large postwar inhalation experiment at Rochester. The design accomplished extremely uniform distribution patterns inside the chamber. (From Leach et al. 1959. Reprinted with permission of *American Industrial Hygiene Association Journal*, Akron, Ohio.)

Fortunately, the experimenters had the vision to hold groups of animals for postexposure study. Some were used to determine pulmonary clearance of the accumulated deposit. It was much slower than clearance after a single exposure. Other animals were held for as long as six years postexposure to look for long-term pathology. The patience of these investigators, especially after the demands of the five-year exposure routine, must be admired, as must the vision of the AEC in providing continued financial support. There is no substitute for actual measurement of long-term distributions and effects.

The patience and effort put into this experiment paid off. Pulmonary fibrosis, comparable to that seen after plutonium inhalation, noted in the lungs of monkeys even before the end of the five-year exposure period, developed markedly during the postexposure years. The lymph nodes, which were literally loaded with uranium, also showed combinations of fibrosis and necrosis similar to those seen with $^{238}\text{PuO}_2$ and $^{239}\text{PuO}_2$. But the most interesting finding was the incidence of neoplasms, metaplasia, etc. in the dogs kept for the full term. Although the incidence was not high, the type of lesion seen essentially never occurs spontaneously in the dog. The radiation dose was calculated as over 10,000 rad in the lymph nodes, considerably less in the lungs, but still hardly minuscule. The monkeys, while showing marked fibrotic changes, did not show frank neoplasia.

These results show that it is possible to produce cancer in at least one animal species with natural uranium if exposures are long enough and accumulations

large enough. In a sense, however, they demonstrate how far above the normal "tolerance" level the tissue contents must be to produce neoplasia. Also, the compound must be very insoluble and thus retained for long periods (Morrow, Gibb, and Leach 1966). Contrast for example the rapid clearance from the lung of the closely related uranium trioxide (UO_3) reported by Morrow, Gibb, and Beiter (1972).

Details of the final results of this work can be found in Leach et al. (1973) and are summarized in the fine chapter by Yuile (1973).

B. The Oak Ridge and Related Experiments Using Animals

The Health Physics Division at Oak Ridge National Laboratory (ORNL) has engaged in few animal experiments (except those concerned with the environment). Their interests have been elsewhere. The ORNL Biology Division had more than enough animal work under way for any one installation. But the Health Physics Division did have the Internal Dose Center, and certain specific questions on the distribution and excretion of uranium seemed to require direct determination in animals. Under the initial direction of Mary Jane Cook and later under Bernard Fish and still later in collaboration with Robert Bernard, some ^{235}U studies were undertaken. These were described by Fish (1958, 1961), Fish and Bernard (1961), and by Fish and colleagues in other ORNL reports (e.g., Fish, Payne, and Thompson 1960). The work involved rats primarily but also a few dogs, using both ingestion and inhalation routes. The data were useful primarily for checking out some of the biologic constants being used in the Oak Ridge Information Center for Internal Exposure (Ford 1964).

C. Other Postwar Animal Experiments

Several investigators used the postwar availability of the higher-specific-activity isotopes of uranium to probe into microdistribution and the possibility of a mass effect. The technique of autoradiography was applied in conjunction with conventional analytical methods. These essentially confirmed by more sophisticated methods what had been established in the MED work (Kisielewski et al. 1952; Jones 1966; Walinder, Hammarström, and Billaudelle 1967; Walinder, Fries, and Billaudelle 1967). It is interesting to note that the last papers come from Sweden. Tannenbaum (1951) gives a reference to a British report on uranium toxicology, published in 1943. By and large, however, biological work abroad with uranium was sparse during the period of greatest activity in the United States.

IV. Data On Man

A. Occupational Exposure

Although the uranium industry had both the largest number of potentially exposed persons and some of the worst conditions of exposure during the war years, the incidence of obvious damage from routine exposures is almost nil. Only after accidental releases of moderately large amounts were frank effects seen. There was an extensive bioassay program at all the uranium processing facilities. Excretion of uranium in the urine was regularly measured, and signs of kidney damage such as the presence of cellular debris or elevation of one or more of constituents such as amino acids, nonprotein nitrogen, albumin, catalase, etc., were regularly checked on. The incidence of these indicators of

damage was relatively low. As a result, it began to be concluded that natural uranium was less toxic to humans than the animal data predicted.

This conclusion, even after these many years, is not a certain one. As brought to light at an AEC symposium on uranium in 1958 (AEC 1959) and expanded upon by Eisenbud (1959), the lung burdens in personnel exposed to insoluble uranium were far below what would be predicted from the measurements of exposure (i.e., the amounts in air). Such information came from post-mortem autopsy data (Eisenbud and Quigley 1956; Donoghue et al. 1972; and summarized by Hursh and Spoor 1973). Also, less retention of soluble uranium than expected was reported for autopsy specimens from an employee who had worked with uranium hexafluoride and died of a coronary thrombosis (Butterworth and McLean 1955).^(a) Further data are given by Quigley, Heatherton, and Ziegler (1959) and Marks (1975).

Unfortunately, and despite the large number of potential cases and situations available for examination, the presence of a truly significant difference in the toxicity of uranium in man compared to several animal species studied cannot be separated from difficulties in the characterization of the exposures. The air sampling methods used in the days of "high" exposures were not very selective as to particle size. Thus, a significant portion of the apparent exposure may have been to nonrespirable particles. And now that the sampling operations are fully capable of detailed particle-size analyses, the operations have become so clean that exposures sufficient to produce toxic effects are limited to the rare accidental releases! The most recent symposium on uranium has highlighted this point (see Eisenbud 1975).

It could be imagined that retrospective analyses and some sophisticated epidemiology applied to the wartime plants and personnel would have solved these problems. But as Eisenbud vividly pointed out at the ERDA symposium, the effort has been weak indeed. He adheres to the view that uranium is clearly less toxic in man than the animal studies indicated. But he also highlighted the frustrations of trying to prove this by pointing out that the literature from animal studies amounted to several thousand pages between 1958 and 1975, but the epidemiologic literature at the time of his paper did not exceed twenty-five pages. Also, the last epidemiologic data to appear seem to be more than twenty years old.^(b)

At long last, a Uranium Registry was established officially in 1978 (Marks 1979). This will operate in much the same fashion as the older Transuranium Registry (more in chapter 16). It remains to be seen if this effort can salvage some of the opportunities missed to learn the true health status of the many hundreds of workers who handled uranium in the production chain^(c) from 1943 to 1954. Why it took so long for the message to get through will always remain a puzzle.^(d)

(a) See also later review by Butterworth (1959).

(b) This author's experience in trying to track down the records of uranium workers for a National Council on Radiation Protection (NCRP) committee was equally frustrating until recently.

(c) This does not include the uranium miners, which are a separate group with a very different problem.

(d) In the early 1980s, epidemiologic studies of populations such as those that worked at the Tennessee Eastman Plant in Oak Ridge were mounted, and early reports have appeared. So far, no abnormal incidence of the potential effects has come to light (more in chapter 16).

There were, of course, a few accidental overexposures which have been reported. Howland reported a wartime accident in which UF_6 , UF_2F_2 , and HF were involved. There were two fatalities and three serious injuries (Howland 1949). But the problem was largely the corrosive HF and F,^(a) and only minimally the uranium.^(b) Exposures more directly relatable to uranium were presented by Fish (1958, 1961), Schultz (1966), Saxby et al. (1964), and Ronen (1969). All of these are considered in some detail by Hursh and Spoor (1973), and, in general, the only conflicts with animal data were occasional long retention times in the body or in lungs and, with the latter, considerable excretion via feces.

There were also instances where workers handling the higher-specific-activity isotopes via enriched uranium showed above-tolerance urinary excretion levels.

B. Planned Administrations

1. Intravenous Injection

a. Rochester Study

As part of the MED effort at Rochester, Bassett and coworkers (1948) carried out a study on hospital patients. Six subjects were selected and placed in the metabolic ward. They were in sufficiently good health that the results seemed unlikely to be vitiated by their disease. Yet, they were clearly in a position to benefit from continued hospitalization. The aim was primarily to check the metabolism of uranium (i.e., distribution and excretion) and not effects except incidentally. The subjects received uranyl nitrate, a soluble salt, enriched with ^{234}U and ^{235}U to make measurements easier with the small quantities involved. But to be doubly sure that the levels were below the threshold for damage, renal function tests were applied in depth to some, in part to all. The doses ranged from 6 μg to 70 $\mu\text{g}/\text{kg}$ of body weight.

The metabolic data indicated rapid urinary excretion and no sharp conflicts with the animal data. Only at the 70- $\mu\text{g}/\text{kg}$ level was there a slight rise in urinary catalase and protein suggesting that threshold kidney damage had occurred. The effect was transient. This experiment has been described and interpreted in depth by Hursh and Spoor (1973) and will be considered again in chapter 16.

In the early postwar years, Terepka, Toribara, and Neuman (1965) wished to check in man the evidence obtained earlier in animal work—that the handling of uranium by bone might be an indicator of skeletal metabolic disorders. Three controls and seven patients with bone disorders received 30 μg of soluble (hexavalent) uranium. Retention was regarded as a function of the relative amount of exchangeable bone, especially when compared with calcium. The results helped distinguish the contributions of bone accretion and bone resorption to the disease at hand since, of course, the uranium enters bone in exchange for calcium.

b. The Boston-Oak Ridge Intravenous Injections

The background for this project lies in the hope of using neutrons for radiation therapy. Some trials had been carried out by Dr. Lee Farr and associates at the

(a) Very recently, the information from these cases has been re-examined and a possible long-term role of uranium suggested. (Kathren, personal communication 1985).

(b) The production of large quantities of compounds in which uranium was combined with fluorine led to a detailed study of fluorine and fluoride toxicity in the Rochester MED work. I have chosen to omit this as not bearing directly on internal emitter toxicology.

Medical Division, Brookhaven National Laboratory in which boron salts were given to patients with advanced brain tumors, and the head area was then exposed to a neutron beam from the old Brookhaven reactor or "pile." If there were sufficient localization of the boron in tumor tissue, the neutron beam might produce specific therapy within the tumor by the n, α reaction.^(a) The results were disappointing.

Dr. William H. Sweet at MGH conceived a different approach. If partially enriched uranium would concentrate in tumor tissue, the neutron beam might produce highly specific and localized damage by the production of fission fragments. Meanwhile, the Health Physics Division at Oak Ridge National Laboratory was interested in better data on the metabolism of hexavalent uranium in man. There ensued a collaborative effort between Oak Ridge and the Department of Neurosurgery at the Massachusetts General Hospital and the Veterans Administration Hospital in Boston, whose justification was the possible benefit of the neutron capture therapy to the patients.

Eight patients who were in terminal phases of severe central nervous system disease were studied. Six were injected with a uranyl nitrate solution enriched in ^{234}U and ^{235}U , two were injected with tetravalent uranium as UCl_4 . The doses varied from 0.097 to 0.28 mg uranium per kilogram and thus were at the upper end of the scale, considerably higher than in the wartime study at Rochester. (Enough uranium had to be present to give some hope for the neutron capture therapy.)

There was not enough concentration of the uranium in tumor tissue to encourage further forays in the therapeutic realm. But a very complete effort was made to find out as much as possible about the metabolism of uranium in these patients. The results are given in detail by Luessenhop et al. (1958), and in somewhat abbreviated form by Struxness et al. (1956) at the First International Conference on the Peaceful Uses of Atomic Energy. They also are analyzed and compared with other studies by Hursh and Spoor (1973). The metabolism data were considered in the context of maximum permissible concentrations by Bernard (1958).

In general, the experiment agrees with the other intravenous studies and with the animal data, particularly those from the laboratory rat. The parlous clinical condition of the Boston patients would have raised questions of validity of the results had they differed markedly, so it is fortunate they are in general agreement. Since several of the Boston patients died within days or weeks after the injection, it was possible to get autopsy material while there was still enough uranium present to be measured. This represents one of the few instances in man where tissue contents could be measured after a known dose in contrast to the great uncertainties of the exposure in the usual occupational situation as detailed in a previous section. This may be the most significant contribution of this rather heroic experiment. The data again indicate that the major conclusions of the animal work apply to humans, at least when the uranium is received by intravenous injection and one considers primarily distribution and excretion.

2. Other Planned Administrations

The administration of uranium as a therapeutic agent in the nineteenth and early twentieth centuries was usually oral. These uses are summarized by Hodge

(a) Boron has a high cross section for neutron capture and could theoretically provide a latent source of radiation in situ. (See chapter 20.)

(1973) and by Hursh and Spoor (1973). Surprisingly large doses seemed to be tolerated in some individuals. Yet, when Butterworth (1955) gave a dose lower than many of these to a volunteer subject, there was a violent gastrointestinal disturbance. It was speculated that the difference may lie in the dosage regimen since the early patients received several doses in ascending size and may have developed tolerance to it, or it may have been a case of high sensitivity.^(a)

Hursh et al. (1969) conducted an oral absorption study on four hospital patients using uranyl nitrate hexahydrate at 10.8 mg uranium dose. They measured urinary and fecal excretion and used the data in retrospect to interpret the reports from the early therapeutic administrations. Also, the low absorption from the gut found in the animal work was confirmed in man, although the figure was not as low as the then-current recommendations of ICRP and NCRP (see chapters 9 and 16).

Harris (1961) did a single experiment involving inhalation of uranium compounds by man. There were twelve periods of inhalation of UO_3 and five periods, all short, of inhalation of UF_4 . The purpose of the experiment was to check on the findings in industry already alluded to that showed a baffling lack of effects after exposures, which were presumably high enough to cause frank damage. This was a complicated and potentially very useful experiment. Unfortunately, the results were equivocal because of discrepancies in the balance sheet for uranium. The author was not able to repeat the work with other subjects. Hence, for direct measurement of metabolism and tissue burdens with known doses administered to man, we have no data for the inhalation route of entry. This is unfortunate in view of the importance of the inhalation route.

3. Commentary on Planned Administrations in Man

These experiments yielded enough information to support the view that the way man handles uranium and his reactions to it are not widely different from the predictions of the animal experiments. They are a unique resource in many respects. They were done when the use of hospital patients giving "informed consent" and of volunteer subjects, including frequently the investigator himself, was easier to arrange. Although there is no evidence that these administrations were in any way harmful or ill-considered at the time, it is difficult to imagine a present-day "human use" committee approving them. It is, thus, doubtful if we will ever have more of the same kind of information. We must, therefore, be content with data from normal industrial uses or the rare accidental overexposure. It may be fortunate that the current hysteria regarding any kind of radiation exposure would assure that ample information would be gathered from any such incidents. But barring these, and they are not going to be numerous, we will need to use what we have and whatever the new epidemiologic studies can garner from the depths of the past.

V. The Higher-Specific-Activity Isotopes and Enriched Uranium

In sharp contrast to the massive attack on the toxicology and all other aspects of natural uranium, only a token biomedical effort was made during the MED days to study the effects^(b) of ^{232}U , ^{233}U , ^{234}U , ^{235}U , and natural uranium at various

(a) Development of tolerance to uranium is a well-established phenomenon. It was shown in the MED work and described in detail in NNES volumes (Voegtlin and Hodge 1949, 1953).

(b) Use of, for example, ^{233}U as a tracer was much more common.

degrees of enrichment with ^{235}U and accompanying isotopes. It seems to be impossible to find a written statement as to why this was so. One can only surmise that the parallel studies of other alpha emitters, particularly plutonium and, to a lesser extent, radium and polonium, going on in the MED laboratories were considered directly applicable to possible radiation effects from the alpha-emitting uranium isotopes of higher specific activity. There was one study in the postwar period—probably initiated late in the war—that stands out as a classic. It will be taken up presently. Nevertheless, particularly in view of current interests in uranium-based rather than plutonium-based fuel cycles, the lack of attention to this subject left a significant gap in our knowledge for many years.

There was no lack of calculations for allowable concentrations of the various uranium isotopes based on radioactivity. For all but natural uranium, these were done basically by calculation of alpha dose or by empirical comparison with ^{226}Ra . An important problem was the determination of that point in the enrichment process where potential radiation dose instead of potential chemical toxicity becomes controlling. As a rule of thumb, the transition point was taken as 5% to 8% by weight ^{235}U (Ford 1964). Spoor and Hursh (1973) examine this problem in depth. They show that using specific alpha activity, and assuming that the proportion of ^{234}U to ^{235}U remains constant in the course of enrichment, the critical organ changes from kidney to bone (and by definition from chemical to radiation effects) at about 16% enrichment. If an alternative assumption is made, i.e., the isotope proportions are those that would result from the diffusion of uranium hexafluoride according to the ideal gas laws, the shift comes at about 8.5% enrichment. The rule-of-thumb figures probably represent a conservative interpretation from these.

There was some interest during the MED days as to whether or not ^{233}U was metabolized like ^{238}U . Tannenbaum (1945) reported that it was, and his paper was expanded and reproduced as paper 7 in the Tannenbaum book (1951). This finding lent support to the widespread use of the shorter-lived isotopes, especially ^{233}U , as a tracer for natural uranium. Quite small amounts could be detected by virtue of the great sensitivity of radioisotope detection and measurement.

Except for a very small experiment at Rochester on effects of ^{233}U on bone resorptive processes (Voegtlin and Hodge 1953, p. 2401), effects studies seem to have been limited to those at the Argonne National Laboratory of the toxicity of several alpha emitters and beta-gamma emitters relative to ^{226}Ra . The results first appear as a project report by Brues (1951) and in detail by Miriam Finkel in the open literature (1953, 1956). The effects reported were development of bone tumors and average survival time in CF1 mice. Uranium-233 was more effective on the basis of microcuries/kilogram administered dose than ^{226}Ra but considerably less effective than ^{239}Pu . When the effectiveness ratio is calculated on the basis of radiation dose, it is more nearly equal between ^{233}U and ^{226}Ra . But the many assumptions necessary for such calculations led Dr. Finkel to hold steadfastly to administered dose as the most valid criterion—in the tradition of classical toxicology.^(a)

(a) As described in chapter 1, a later, better radium experiment was conducted by Finkel and published in 1969 (Finkel, Biskis, and Jinkins 1969). While the comparison is not direct (i.e., in the same experiment) as it was in the earlier work, use of the data for ^{226}Ra from this later experiment makes it and ^{233}U appear even more similar in effectiveness.

It is to be regretted that the extremely important comparison of bone seekers, which was followed up by the large experiment on dogs at the University of Utah (to be discussed in later chapters), was not repeated for ^{233}U or any of the other pertinent uranium isotopes. Nevertheless, the Finkel experiment was well conducted; the data have been re-examined from the original protocols by Durbin, Wrenn, and Stannard (1975), and the conclusion that ^{233}U is less effective than ^{239}Pu seems established fully.

In the 1980s, the results of a program at Pacific Northwest Laboratory^(a) conducted by John Ballou have begun to appear. This considers all members of the ^{232}U decay series and some of the higher-specific-activity uranium isotopes. As with many such new enterprises, it was necessary to sort out the in-vivo relationships of parents and daughters in the decay series. This was described very recently at the thirtieth annual meeting of the Health Physics Society (Ballou and Case 1985). Other descriptions have appeared in PNL annual reports (e.g., Ballou 1985, which considers the results of inhaled ^{233}U - ^{232}U intake and oxide fuels and ^{231}Pa). This work should go far to fill the gap in our knowledge of behavior and effects of isotopes of uranium other than ^{238}U , especially those in the thorium fuel cycle left by the inactivity since the publication of Finkel's mouse experiments.

VI. Postscript

The story told in the above sections became almost dogma. Indeed, it was, when this chapter was first written.^(b) Little new work was done with uranium for many years. After all, was it not the most thoroughly investigated of the heavy metal toxins? Also, conditions in the plants improved greatly so that exposures declined markedly, and gradually the number of employees decreased. Only at Rochester was there some lingering experimental work. In the last decade, beginning with the symposium sponsored by ERDA in 1975, and especially in the last five years, there has been a resurgence of interest in uranium and new biomedical work. Some of it is described in chapter 15 and later. We will consider two aspects here.

The rudimentary metabolic models for uranium possible from the earlier work described in this chapter have been greatly expanded and improved. This was brought about partly by the needs for setting drinking water standards, but was far from limited thereto. The New York University (NYU) group began the modeling effort, particularly M. E. Wrenn and his graduate students. It continued at the University of Utah when Wrenn moved there. He was joined early by P. W. Durbin, at the University of California, Berkeley, who had begun work independently on a uranium metabolic model, partly to meet the needs of an NCRP committee, and partly via a long-standing interest in metabolic models. The resulting publications show the evolution from simple to complex and how important the right model can be to standard setting and to understanding what is going on in the body (Durbin and Wrenn 1975; Wrenn, Lo Sasso, and Durbin 1977; Roswell and Wrenn 1980; Wrenn et al. 1985; Durbin 1986).

The last named reference is a finely crafted summary of the entire history of uranium modeling, which Durbin presented in August 1984 at a workshop on

(a) Operated at Hanford for the U.S. Department of Energy by Battelle Memorial Institute. This institution is variously referred to here as Pacific Northwest Laboratory (PNL); Battelle, Pacific Northwest Laboratories; Battelle; and Battelle-Northwest (BNW).

(b) This was the first chapter written and had the earliest cutoff date (see preface).

uranium held in Richland, Washington. The proceedings of this workshop were published in 1986. Wierm was on the same program and presented details of the modeling he and Durbin had been engaged with as well as some other aspects of uranium metabolism and standards.

Meanwhile, back at Rochester, where it all started and where it never stopped completely, Paul Morrow set about answering some questions posed by a contract with the Nuclear Regulatory Commission (NRC). His results indicated greater chemical toxicity in the dog than the work quoted in earlier sections of this chapter and taken up in chapters 16 and 21. Indeed, his major report to the NRC suggested that the bench-mark threshold value for damage from uranium in the kidney ($3 \mu\text{g/g}$) might be too high (Morrow et al. 1982). He and his group applied a battery of much more sophisticated tests for kidney damage than was available in the days concentrated upon in this chapter. They found evidence for damage at blood or urine levels expected to be associated with $3 \mu\text{g/g}$ kidney. Furthermore, they showed that kidney damage was not as strictly limited to the proximal tubule as the earlier work showed. Finally, they addressed the phenomenon of tolerance. While the phenomenon was definite, their work indicated that it is much more complex than described earlier. There are different degrees of tolerance and different time courses in different organs and under different regimes.

Morrow was also present at the uranium workshop in August 1984 mentioned above. His paper provides an excellent review of how work in the recent past and ongoing is showing the degree to which we may have oversimplified the phenomena of uranium toxicology, both chemical and radiation (Morrow 1986). It is far from a closed book!

Such is the nature of biomedical research. Nothing was basically wrong with the picture described earlier; it has, however, been sharpened and refined, and this will probably continue to occur.

VII. Summary and Commentary

Biological effects of natural uranium were described in the 1820s. By 1860, it was being used therapeutically in homeopathic medicine for the treatment of diabetes. It was also used experimentally for the production of kidney changes resembling clinical nephritis. However, the true therapeutic benefits of uranium, unlike radium, were small compared to its potential for untoward health effects.

Even after it was demonstrated that uranium is radioactive, the bulk of the biomedical research focused on its action as a chemical toxin to the kidney. The effects of the radioactivity were considered less important because of the very low specific activity of natural uranium.

Despite a considerable backlog of research from the mid-1880s into the 1930s, the needs of the World War-II development of atomic energy were not met, primarily because the earlier work involved soluble compounds, while the expected compounds in the new enterprise were, many of them, quite insoluble. When the decision was made to proceed with the nuclear fission bomb project, it was realized that a large number of workers would be involved at the various steps. A major effort was put into making the workplaces safe by both application of safety measures and what has been characterized as "the most comprehensive experimental investigation of an industrial poison ever carried

out by any group of scientific workers in such a short time" (Voegtlin and Hodge 1949).

Two centers were responsible for most of the work on uranium during the Manhattan Engineer District days. These were the MED project at the University of Rochester Medical School, Rochester, New York, and a segment of the Metallurgical Laboratory at the University of Chicago, primarily the Michael Reese Hospital. Pioneer work was done at the Crocker Laboratory, University of California at Berkeley. In the postwar period, the Atomic Energy Project at Rochester mounted a long-term inhalation study, the Argonne National Laboratory at Chicago carried a few important residual problems to completion, and Oak Ridge National Laboratory joined for some studies. There were also scattered special studies at other laboratories, but, with these exceptions, work on uranium was much less emphasized in the post-World-War-II period than it had been during the MED days. This contrasts sharply with most other phases of the radionuclide research that were carried forward and amplified along lines very similar to the war work.

The work made it clear that, while uranium is a specific kidney poison, its primary storage depot in the body is bone, except for inhaled insoluble compounds, where the major storage depot can be lung. The solution chemistry was worked out in detail, biochemical aspects were very completely characterized, and at least two major lines of postwar investigation grew directly out of the uranium work. These were the chemistry and biochemistry of bone, which were shared with the earlier and continuing work on radium; and cell surface enzymes, whose discovery and characterization came directly from attempts to understand how uranium produced its effects on cells.

On the whole, the work has stood the test of time very well. Only one major area seems to have been neglected: effects of the higher-specific-activity isotopes and enriched uranium. While the work that was done has been very useful and informative, present interest in new fuel cycles makes the relative paucity, until very recently, of data on effects of ^{233}U , ^{234}U , and ^{235}U especially noticeable. On the other hand, the higher-specific-activity isotopes have been very useful as tracers in biochemical and pathological investigations.

An important area for future work is epidemiologic study of the large populations of uranium workers. At long last, this has begun and deserves attention and support in the future. After all, uranium workers were by far the largest population exposed occupationally in the MED and early postwar years. Fortunately, a retrospective study of the workers at the Tennessee Eastman Plant, operated in Oak Ridge during the MED days, has been undertaken by a group at Oak Ridge Associated Universities. This is fortunate because this operation seems most likely to have air concentration data, etc., that can be used now. It is anticipated that the publications will be appearing soon.

Not covered in this chapter, except for one experiment, is the large effort devoted to inhalation studies at Rochester, especially during World War II. These are reserved for chapter 9.

As with radium, there has been considerable interest in the concentrations of uranium in environmental media: water from various natural sources, air and water from natural sources, and manmade sources such as uranium mill tailings. Wide ranges of concentration have been found to occur naturally. There is, however, even less chance of demonstrating any biomedical effects in the populations concerned, except in the uranium miners, and theirs is not a uranium problem, as we will see in chapter 3.

Recently there has been much movement toward regulating, at very low levels, the amount of uranium in drinking water. Despite all of the research completed, there seems still to be debate about whether the chemical toxicity or potential long-term radiation effects should control the choice of limiting concentration (more in later chapters).

References

- AEC. See Atomic Energy Commission.
- Atomic Energy Commission, Health and Safety Laboratory. 1959. In *Occupational health experience and practices in the uranium industry*, HASL-58. Proceedings of a symposium held in New York City, October 15-17, 1958. Washington, D.C.: Department of Commerce, Office of Technical Services.
- Ballou, J. E. 1985. Toxicity of thorium cycle nuclides. In *Pacific Northwest Laboratory Annual Report for 1984 to the DOE Office of Energy Research, Part 1 Biomedical sciences*, PNL-5500, pt. 1, pp. 35-37. Richland, Wash.: Pacific Northwest Laboratory.
- Ballou, J. E. and A. C. Case. 1985. In vivo parent/daughter relationships in the ^{232}U decay series. In *Proceedings of the 13th annual meeting of the Health Physics Society* held in Chicago, May 1985. WPM-C5, p. 60 of abstracts.
- Barron, E. S. G. 1951. The mechanism of action of uranium and the transport of uranium to the tissues. Chapter 7 in Tannenbaum 1951, pp. 40-44.
- Barron, E. S. G., J. A. Muntz, and B. Gasvoda. 1948. Regulatory mechanisms of cellular respiration. I. The rôle of cell membranes: Uranium inhibition of cellular respiration. *J. Gen. Physiol.* 32:163-78.
- Bassett, S. H. et al. 1948. The excretion of hexavalent uranium following intravenous administration. II. Studies on human subjects. UR-37. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Berke, H. L., A. Rothstein, C. W. Bishop, E. Roberts, and W. Mann. 1953. Metabolic studies. Chapter 23 in Voegtlin and Hodge 1953, pp. 1841-1910.
- Bernard, S. R. 1958. Maximum permissible amounts of natural uranium in the body, air and drinking water based on human experimental data. *Health Phys.* 1:288-305.
- Bloor, W. R. and W. F. Neuman. 1949. The fluorophotometric determination of uranium. In chapter 2 in Voegtlin and Hodge 1949, pp. 150-63.
- Brues, A. M. 1951. *Comparative chronic toxicities of radium and plutonium*. ANL-4625, pp. 106-24. Argonne, Ill.: Argonne National Laboratory.
- Butterworth, A. 1955. The significance and value of uranium in urine analysis. *Trans. Assoc. Ind. Med. Off.* 5:36-43.
- Butterworth, A. 1959. Human data on uranium exposure. In Atomic Energy Commission, Health and Safety Laboratory 1959, pp. 41-46.
- Butterworth, A. and A. S. McLean. 1955. *Observations on the metabolism of soluble uranium in humans*. IGO-R/R-8. United Kingdom Atomic Energy Authority.
- Donoghue, J. K., E. D. Dyson, J. S. Hislop, A. M. Leach, and N. L. Spoor. 1972. Human exposure to natural uranium: A case history and analytical results from some post-mortem tissues. *Br. J. Ind. Med.* 29:81-89.
- Dounce, A. L. 1949. The mechanism of action of uranium compounds in the animal body. Chapter 15 in Voegtlin and Hodge 1949, pp. 951-91.
- Dounce, A. L. and T. H. Lan. 1949. The action of uranium on enzymes and proteins. Chapter 13 in Voegtlin and Hodge 1949, pp. 759-888.
- Dounce, A. L., E. Roberts, and J. H. Wills. 1949. Catalasuria as a sensitive test for uranium poisoning. Chapter 14 in Voegtlin and Hodge 1949, pp. 889-950.
- Durbin, P. W. 1986. Metabolic models for uranium. In *Biokinetics and analysis of uranium in man*, USUR-05 HEHF-47, pp. F-1-F-65. Proceedings of a uranium workshop sponsored by the U.S. Uranium Registry held in Richland, Wash., August 8-9, 1984. Richland, Wash.: Hanford Environmental Health Foundation.

- Durbin, R. W. and W. E. Wharm. 1975. Metabolism and effects of uranium in animals. In *Conference on occupational health: experience with uranium*, ERDA-95, pp. 67-129. Held in Arlington, Va., April 28-30, 1975. Washington, D.C.: U.S. Energy Research and Development Administration.
- Durbin, R. W., W. E. Wharm, and J. N. Stannard. 1975. Personal conference at Berkeley, Calif.
- Eisenbud, M. 1959. Discussion of apparent anomalies in lung retention of uranium. In *Atomic Energy Commission Health and Safety Laboratory 1959*, pp. 252-53.
- Eisenbud, M. 1975. Early occupational exposure experience with uranium processing. In *Conference on occupational health: experience with uranium*, ERDA-95, pp. 8-24. Held in Arlington, Va., April 28-30, 1975. Washington, D.C.: Energy Research and Development Administration.
- Eisenbud, M. and J. A. Quigley. 1955. Industrial hygiene of uranium processing. *Arch. Ind. Health* 14:122-22.
- Ferretti, R. J. and S. Schwartz. 1946. *Uranium distribution studies*. Metallurgical Laboratory report, CM-2595. Also paper 14 in Tammendaum 1957, pp. 274-32.
- Finkel, M. P. 1953. Relative biological effectiveness of radium and other alpha emitters on CF₁m. female mice. *Proc. Soc. Exp. Biol. Med.* 83:494-98.
- Finkel, M. P. 1956. Relative biological effectiveness of internal emitters. *Radiology* 67:665-72.
- Finkel, M. P., B. O. Boske, and P. B. Jenkins. 1959. Toxicity of radium-226 in mice. In *Radiation-Induced Cancer*, IAEA-SW-78B/37, pp. 362-97. Proceedings of a symposium held in Athens, April 28-May 2, 1959. Vienna: International Atomic Energy Agency.
- Fish, B. R. 1956. Single acute intake of UO₂ aerosol. *Oak Ridge Laboratory annual report*, ORNL-2590, p. 148. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Fish, B. R. 1961. Inhalation of uranium aerosols by mouse, rat, dog and man. In *Inhaled particles and vapors*, ed. C. N. Davies, pp. 151-56. Proceedings of an international symposium held in Oxford, March 29-April 7, 1960. London: Pergamon Press.
- Fish, B. R., J. A. Payne, and J. L. Thompson. 1960. Ingestion of uranium compounds. *Oak Ridge National Laboratory annual report*, ORNL-2994, pp. 263-72. Oak Ridge, Tenn.: Oak Ridge National Laboratory, Health Physics Division.
- Ford, W. R. 1954. Comments on intake guidelines for various isotopes and isotopic mixtures of uranium. *Oak Ridge National Laboratory annual report*, ORNL-3527, pp. 202-06. Oak Ridge, Tenn.: Oak Ridge National Laboratory, Health Physics Division.
- Friedel, H. 1951. History of biomedical work in Warrenton Engineer District. Impregnation. [Manuscript seen courtesy of Dr. Friedel.]
- Grolier, J. E. 1973. Physical and chemical properties of uranium. Chapter 2 in Hodge, Stannard, and Hursh 1973, pp. 69-164.
- Hamilton, J. C. 1948a. The metabolic properties of plutonium and allied materials, studies with U²³⁹. In *Quarterly report*, WCR-457, pp. 6-51. Berkeley, Calif.: Univ. of Calif. Radiation Laboratory.
- Hamilton, J. C. 1948b. The metabolic properties of plutonium and allied materials, tracer study with uranium. In *Quarterly report*, WCR-495, p. 11. Berkeley, Calif.: Univ. of Calif. Radiation Laboratory.
- Hamilton, J. C. 1948c. The metabolic properties of plutonium and allied materials, tracer study of uranium-235. In *Quarterly report*, WCR-45, p. 15. Berkeley, Calif.: Univ. of Calif. Radiation Laboratory.
- Harris, W. B. 1961. Experimental clearance of uranium dust from the human body. In *Inhaled particles and vapors*, ed. C. N. Davies, pp. 209-15. Proceedings of an international symposium held in Oxford, March 29-April 7, 1960. London: Pergamon Press.
- Hodge, H. C. 1953a. Mechanism of inhibition of glucose metabolism by uranium. Chapter 2 in Voegtlin and Hodge 1953, pp. 2405-08.
- Hodge, H. C. 1953b. Studies in cell metabolism. In chapter 29 in Voegtlin and Hodge 1953, pp. 2403-23.
- Hodge, H. C. 1973. A history of uranium poisoning (1824-1942). Chapter 11 in Hodge, Stannard, and Hursh 1973, pp. 5-61.

- Hodge, H. C., J. N. Stannard, and J. B. Hursh. 1973. Uranium, plutonium, transplutonic elements: *Handbook of experimental pharmacology*, new series, vol. 36. New York: Springer-Verlag.
- Kinward, J. W. 1949. Studies on human exposures to uranium compounds. Chapter 16 in Voegtlin and Hodge 1949, pp. 993-1017.
- Hursh, J. B. and N. L. Spurr. 1973. Data on man. Chapter 4 in Hodge, Stannard, and Hursh 1973, pp. 197-239.
- Hursh, J. B., W. R. Neuman, T. Torigata, H. Wilson, and C. Waterhouse. 1969. Oral ingestion of uranium by man. *Health Phys.* 17: 619-21.
- Jones, E. S. 1966. Microscopic and autoradiographic studies of distribution of uranium in the rat kidney. *Health Phys.* 12: 1487-51.
- Katz, E. J., L. C. Holt, and S. Schwartz. 1946. The effect of uranium exposure on urinary catalase excretion. *Metalurgical Laboratory report*, CH-3514. Also paper 115 in Tannenbaum 1951, pp. 281-89.
- Kisilevski, W. E., W. C. Faraghat, W. P. Norris, and J. S. Arnold. 1952. The metabolism of uranium-233 in mice. *J. Pharmacol. Exp. Ther.* 104: 462-67.
- Lesch, L. J., E. A. Maynard, H. C. Hodge, J. K. Scott, C. L. Yule, C. E. Sylvester, and H. B. Wilson. 1970. A five-year inhalation study with natural uranium dioxide (UO_2) dust—II. Retention and biologic effect in the monkey, dog and rat. *Health Phys.* 18: 599-612.
- Lesch, L. J., C. J. Speigl, R. H. Wilson, C. E. Sylvester, and K. E. Laurentzsch. 1952. A multiple chamber exposure unit designed for chronic inhalation studies. *Am. Ind. Hyg. Assoc. J.* 20: 18-22.
- Lesch, L. J., C. L. Yule, H. C. Hodge, C. E. Sylvester, and H. B. Wilson. 1973. A five-year inhalation study with natural uranium dioxide (UO_2) dust—II. Postexposure retention and biologic effects in the monkey, dog and rat. *Health Phys.* 25: 229-58.
- Luesenhop, A. J., J. C. Callimore, W. H. Sweet, E. G. Swarress, and J. Robinson. 1952. The toxicity in man of hexavalent uranium following intravenous administration. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* 78: 88-100.
- Markis, S. 1975. A review of the Bell Study. In *Conference on occupational health experience with uranium*, EROA-23, pp. 257-61. Held in Arlington, Va., April 28-30, 1975. Washington, D.C.: U.S. Energy Research and Development Administration.
- Markis, S. 1979. Taped interview, June 11, 1979.
- Morrow, P. E. 1986. Biokinetics and toxicology of uranium. In *Biokinetics and analysis of uranium in man*, USUR-95, HEH-F-47, pp. E-1-E-27. Proceedings of a workshop sponsored by the U.S. Uranium Registry, held in Richland, Wash., August 8-9, 1984. Richland, Wash.: Hanford Environmental Health Foundation.
- Morrow, P. E., E. R. Gibb, and H. D. Beier. 1972. Inhalation studies of uranium trioxide. *Health Phys.* 23: 273-80.
- Morrow, P. E., E. R. Gibb, and L. J. Lesch. 1966. The clearance of uranium dioxide dust from the lungs following single and multiple inhalation exposures. *Health Phys.* 12: 1217-23.
- Morrow, P. E., L. J. Lesch, E. A. Smith, R. W. Gelein, J. B. Scott, H. D. Beier, F. J. Amato, J. J. Picano, C. L. Yule, and T. G. Conster. 1982. Weatholic fire and evaluation of injury in rats and dogs following exposure to the hydrolysis products of uranium hexafluoride. NUREG/CR-2261. Washington, D.C.: U.S. Nuclear Regulatory Commission.
- Mumtaz, J. A., T. P. Singer, and E. S. C. Barton. 1947. Effect of uranium on the metabolism of yeast and bacteria. *Metalurgical Laboratory report*, CH-3716. Also paper 12 in Tannenbaum 1951, pp. 246-67.
- Neuman, W. F. and W. F. Neuman. 1948. The deposition of uranium in bone. II. Radioautographic studies. *J. Biol. Chem.* 175: 711-14.
- Neuman, W. F. 1953. Deposition of uranium in bone. Chapter 24 in Voegtlin and Hodge 1953, pp. 1911-97.
- Neuman, W. F. 1978. Taped interview, May 25, 1978.
- Neuman, W. F. and W. F. Neuman. 1953. *The chemical dynamics of bone mineral*. Chicago: Univ. of Chicago Press.

- Neuman, W. F., M. W. Neuman, and B. J. Mulryan. 1948. The deposition of uranium in bone. I. Animal studies. *J. Biol. Chem.* 175:705-09.
- Neuman, W. F. and G. H. Tishkoff. 1953. Chemistry. In chapter 18 in Voegtlin and Hodge 1953, pp. 1087-1138.
- Neuman, W. F., R. W. Fleming, A. B. Carlson, and N. Glover. 1948a. The fluorophotometric determination of uranium in biological material. *J. Biol. Chem.* 173:41-52.
- Neuman, W. F., M. W. Neuman, E. R. Main, and B. J. Mulryan. 1948b. The deposition of uranium in bone. III. The effect of diet. *J. Biol. Chem.* 175:715-19.
- Neuman, W. F., M. W. Neuman, E. R. Main, and B. J. Mulryan. 1949a. The deposition of uranium in bone. IV. Adsorption studies in vitro. *J. Biol. Chem.* 179:325-33.
- Neuman, W. F., M. W. Neuman, E. R. Main, and B. J. Mulryan. 1949b. The deposition of uranium in bone. V. Ion exchange studies. *J. Biol. Chem.* 179:335-40.
- Neuman, W. F., M. W. Neuman, E. R. Main, and B. J. Mulryan. 1949c. The deposition of uranium in bone. VI. Ion competition studies. *J. Biol. Chem.* 179:341-48.
- Quigley, J. A., R. C. Heatherton, and J. F. Ziegler. 1959. Studies of human exposure to uranium. In Atomic Energy Commission, Health and Safety Laboratory 1959, pp. 34-40.
- Price, G. R., R. J. Ferretti, and S. Schwartz. 1953. Fluorophotometric determination of uranium. *Anal. Chem.* 25:322-31.
- Ronen, M. 1969. A case of insoluble natural uranium exposure: A two-year follow-up study. In *Handling of radiation accidents*, STI/PUB/229, pp. 451-57. Proceedings of a symposium held in Vienna, May 19-23, 1969. Vienna: International Atomic Energy Agency.
- Roswell, R. L. and M. E. Wrenn. 1980. An improved model for uranium metabolism in man. In *Research in radiobiology annual report of work in progress in the Internal Irradiation Program*, COO-119-256, pp. 115-32. Salt Lake City: Univ. of Utah Press.
- Rothstein, A. 1953. Studies in cell metabolism. In chapter 25 in Voegtlin and Hodge 1953, pp. 1992-2103.
- Rothstein, A. 1978. Taped interview, May 17, 1978.
- Saxby, W. M., N. A. Taylor, J. Garland, J. Rundo, and D. Newton. 1964. A case of inhalation of enriched uranium dust. In *Assessment of radioactivity in man*, vol. 2, pp. 535-47. Proceedings of a symposium held in Heidelberg, May 11-16, 1964. Vienna: International Atomic Energy Agency.
- Schultz, N. B. 1966. Inhalation cases of enriched insoluble uranium oxides. In *Proceedings of the 1st congress of the International Radiation Protection Association*, K-C-822. Held in Rome, September 6-10, 1960. Oxford: Pergamon Press.
- Schwartz, S. 1951a. Urinary excretion of catalase. Part 2.2 of chapter 6 in Tannenbaum 1951, p. 38.
- Schwartz, S. 1951b. Urinary excretion of coproporphyrin. In part 2.3 of chapter 6 in Tannenbaum 1951, p. 38.
- Scott, L. M. 1973. Environmental monitoring and personnel protection in uranium processing. Chapter 6 in Hodge, Stannard, and Hursh 1973, pp. 271-94.
- Singer, T. P., J. A. Muntz, J. Meyer, B. Gasvoda, and E. S. G. Barron. 1947. *The reversible inhibition of enzymes by uranium*. Metallurgical Laboratory report, CH-3739. Also paper 11 in Tannenbaum 1951, 208-45.
- Spoor, N. L. and J. B. Hursh. 1973. Protection criteria. Chapter 5 in Hodge, Stannard, and Hursh 1973, pp. 241-70.
- Steckel, L. M. and C. M. West. 1966. *Characterization of Y-12 uranium process materials correlated with in vivo experience*. Y-1544-A. Oak Ridge, Tenn.: Union Carbide Corporation.
- Struxness, E. G., A. J. Luessenhop, S. R. Bernard, and J. C. Gallimore. 1956. The distribution and excretion of hexavalent uranium in man. In *Proceedings of the international conference on the peaceful uses of atomic energy*, vol. 10, pp. 186-96. Held in Geneva, August 8-20, 1955. New York: United Nations.
- Tannenbaum, A. 1945. *Distribution of U^{233} in tissues of mice following injection of U^{233} (+6) nitrate*. MDDC-1280. Washington, D.C.: U.S. Atomic Energy Commission.
- Tannenbaum, A., ed. 1951. *Toxicology of uranium*. National Nuclear Energy Series, div. IV, vol. 23. New York: McGraw-Hill.

- Task Group on Lung Dynamics. 1966. Deposition and retention models for internal dosimetry of the human respiratory tract. *Health Phys.* 12:173-207.
- Terepka, A. R., T. Y. Toribara, and W. F. Neuman. 1965. *Skeletal retention of uranium in man*. Presented at the 46th Meeting of the Endocrine Society held in San Francisco, June 18, 1964.
- USAEC. See Atomic Energy Commission.
- Voegtlin, C. and H. C. Hodge. 1949. *Pharmacology and toxicology of uranium compounds*. National Nuclear Energy Series, div. VI, vol. 1, pts. I and II. New York: McGraw-Hill.
- Voegtlin, C. and H. C. Hodge. 1953. *Pharmacology and toxicology of uranium compounds*. National Nuclear Energy Series, div. VI, vol. 1, pts. III and IV. New York: McGraw-Hill.
- Walinder, G., B. Fries, and U. Billaudelle. 1967. Incorporation of uranium. II. Distribution of uranium absorbed through the lungs and the skin. *Br. J. Ind. Med.* 24:313-19.
- Walinder, G., L. Hammarström, and U. Billaudelle. 1967. Incorporation of uranium. I. Distribution of intravenously and intraperitoneally injected uranium. *Br. J. Ind. Med.* 24:305-12.
- Wrenn, M. E., T. Lo Sasso, and P. W. Durbin. 1977. A metabolic model for uranium metabolism in man. In *Radioactivity studies progress report*, sec. 11, COO-3382-16. New York: New York University, Institute of Environmental Medicine Center.
- Wrenn, M. E., P. W. Durbin, B. Howard, J. Lipsztein, J. Rundo, E. T. Still, and D. L. Willis. 1985. Metabolism of ingested U and Ra. *Health Phys.* 48:601-33.
- Yuile, C. L. 1973. Animal experiments. Chapter 3 in Hodge, Stannard, and Hursh 1973, pp. 165-96.

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Capsule Chronology

- 1400 et seq.** Mysterious malady kills miners at early age in mountains around Schneeberg (Saxony) and Joachimsthal (Jachymov) in the Sudetenland, now Czechoslovakia. Called mountain sickness. Known throughout the following centuries.

Most of eighteenth and nineteenth centuries—therapeutic spas booming.

- 1879** Identification of the malady in Schneeberg mines as lung cancer. Thought to be lymphosarcomata. Causation murky.
- 1904** Radon and daughters identified as part of the uranium series. Work with animals begins, especially in Russia and France.
- 1913** Determined that the lung cancers are mostly bronchogenic carcinoma.
- 1920–1930s** Much use of radon generators in hospitals for preparation of radon seeds.
- 1921** Suggestion that radium and radium emanation might be causative agent for cancer in miners taken seriously, but not proven.
- 1924** Measurements of mine air begin. Correlations made between high radon areas and areas of high cancer incidence in the mines. Possibility that airborne radon might be causative agent embraced by Ludewig and Lorensen.
- 1926** Government of Czechoslovakia finally agrees the malady at Joachimsthal (Jachymov) mines is lung cancer. Followed by detailed scientific reports in early 1930s.
“Emanatorium” in use at Copenhagen.
- 1929–1930** Fifty percent of miners dying at Joachimsthal have carcinoma of lung.
- 1932** Lung cancer in miners of Germany and Czechoslovakia designated a compensable occupational disease. This greatly facilitated follow-up.
- 1935** Findeisen indicates nearly all uncombined atoms inhaled will deposit on bronchial epithelium.
Lung modeling begins in earnest.
- 1939–1940** Animal toxicology shows generalized inflammation, hyperemia, etc. from radon, but no lung cancers.
- 1941** First standard for radon promulgated (10^{-11} Ci/l). Evans and Goodman, National Bureau of Standards report.

WORLD-WAR-II YEARS

A relatively quiet period because of other war activities. Animal work by Lorenz at National Cancer Institute. Calculated radiation doses from radon considered too small to account for effects.

Radon measured in storage areas for uranium ore. Concerns develop over radon from uranium mill tailings.

Mitchell (1945) relates magnitude of calculated radiation dose to bronchi of miners to incidence of carcinoma. Other calculations made by Evans in 1950.

- 1950s** Great expansion of uranium mining in the United States.
Concern voiced for health of miners.
Requests made to U.S. Public Health Service for assistance in evaluating mines. PHS^(a) makes recommendations to states.
Problems of dosimetry emphasized.
- 1950-1951** Epidemiologic studies begin in Colorado Plateau area, both mines and mills. Also medical examinations begin, but funding very inadequate.
- 1951** Surveys of mines start. Holaday, Ayer, et al.
Bale's "memo to the files" pointing out greater importance of preformed daughters compared to those formed in vivo. Similar idea found in Ph.D. thesis by J. Harley (1952), published in 1953.
- 1951 and 1954** K. Z. Morgan suggests lowering allowable exposure level for radon.
- 1952** AEC New York Office lends equipment and assistance (Harley, Eisenbud), but AEC not taking direct responsibility.
Control measures by ventilation of mines recommended.
- 1953** Utah surveys all operating mines for radon daughters.
- 1953 et seq.** Extensive animal work at Rochester to analyze role of preformed daughters (Shapiro and Bale).
Animal work at Naval Radiological Defense Laboratory (Cohn).
- Mid-1950 through 1960s** Rochester work with animals. Acute LD₅₀ for radon similar to that for x rays (Morken).
Red cell count never fully recovers after acute radon exposure (Morken and Scott).
Precancerous changes seen in lungs, but no tumors (Scott).
- 1954** Epidemiology team on the Colorado Plateau becomes a discrete entity. AEC office at Grand Junction helps.
- 1954-1965** Uranium mining begins and ends in Canada.
- 1955** Chamberlain and Dyson propose major part of dose to trachea and large bronchi is from preformed RaA.
Seven States Uranium Mining Conference. Need for better dosimetric unit emphasized. Idea of "Working Level" (WL) born. Tending toward 10⁻¹⁰ c/l.
- 1956** Tsivoglou method used widely for evaluating inhalation hazard by measuring individual atmospheric contents of each daughter.
Bureau of the Budget discourages use of federal funds in the uranium mines study.
- 1956 et seq.** Working levels measured in thermal galleries of therapeutic spas.
- 1957** Working level defined in a PHS document and gradually adopted by all concerned.
Extensive medical survey. Increase in lung cancer incidence in miners of Colorado Plateau considered certain.

(a) For abbreviations and acronyms, see Appendix D.

- 1958** Stannard proposes that lung be regarded as a moderately radiosensitive organ.
- 1961** "Governors' Conference" recommendations cause shutdown of some mines.
Sputum cytology program begins.
Many company representatives express disbelief in causation of health problems.
- 1960s** Animal research at Pacific Northwest Laboratory emphasizes role of other agents along with radon and daughters, e.g. uranium ore dust, cigarette smoke, diesel exhaust.
Lung neoplasms definitely seen in dogs.
Modeling lung dose becomes a full-time occupation in some quarters.
Many new instruments devised.
- 1964** Rapid increase in number of lung cancer cases in the mines reported.
Lung cancer incidence in miners six times that of nonminers.
Definitive reviews of epidemiology begin.
- 1965** Radon in natural waters from various parts of the world range from 225,000 pCi/l to barely measurable (Hursh, Rochester)
- 1966** Realization that uranium mill tailings had been used as fill dirt for dwelling foundations, in roads, etc., in Grand Junction and Durango, Colorado. PHS surveys thousands of homes, assisted by AEC. Later a similar situation was found around the phosphate mines in Florida.
- 1967** Congressional Hearings under Joint Committee on Atomic Energy.
Federal Radiation Council presents reports and recommendations—tentatively 1 WL (12 WLM per year).
- 1969** More Congressional hearings.
Czech epidemiologic study reported.
Evans "Engineers Guide" to behavior of radon daughters published.
- 1970** Bair's review of dilemmas of animal work with radon (Gatlinburg Symposium in 1969).
- 1970-1971** Interagency Uranium Mining Group report.
Secretary of Labor Wirtz decrees exposure level in mines will be 0.3 WL (4 WLM per year).
Sudden reversal from skepticism and inadequate support to a veritable bandwagon to protect the miners' health.
- 1970s** Animal research at CEA, Razès (Limoges) France. Lung tumors found in rats.
- 1972** Surgeon General issues guidelines for remedial action in areas of mill tailings use (0.05 WL for action, 0.01 to 0.05 WL advisory).
- 1973** More interest developing in doses to populations living near hot springs.
- 1976** Czech epidemiologic study reported.

- 1977-1981** Risk estimates attached to radon exposures (UNSCEAR, BEIR III, Evans et al.).
- Reviews of epidemiology of several groups of miners in the United States, Canada, and Europe.
- 1982** Chromosome aberration frequency reported for inhabitants and workers at Badgastein (Pohl-Rüling). Health-spa population declared "promising" for epidemiologic study (Wrenn).
- 1983 et seq.** Great increase in concern over population exposures to radon and daughters indoors. A major current enterprise.
- 1984** Two NCRP reports published on radon in the environment and a general review of radon. Suggestion of 2 WLM made for triggering structural alterations or cleanup of dwellings.

Chapter 3

Radon and Radon Decay Products: The Saga of the Uranium Miners

Overview

The uranium miner saga predates all of the other areas of investigation considered in this book, even that of radium. However, understanding of the causal relationships was very slow to come. Only in the post-World-War-II decades has it been possible by a mixture of laboratory research and epidemiologic studies to establish cause and effect on a firm basis and establish some rough quantitative relationships. It is a field full of dilemmas and frustrations, some of which still persist. This chapter, like the one on radium, cannot begin with or just before the Manhattan Engineer District (MED) operations. In fact, radon problems were almost totally ignored by the MED. We must go back to Europe in the Middle Ages to develop a connected story.

The chapter reviews the highlights of the miners' history in Schneeberg and Joachimsthal, the gradual development of ideas on causation, the work of Lorenz and colleagues in World War II, and then in some detail the very active period in the United States from about 1950 on involving both laboratory research and field studies. Because of the strong political overtones of the problem, the chapter digresses briefly into some of the reasons such a serious problem was allowed to develop despite previous knowledge. The parallel work with other miner populations and work abroad is reviewed briefly in order to provide a wide picture.

Because of the analogy to the iatrogenic radium cases examined in chapter 1, the chapter reviews also the story of the therapeutic spas, therapeutic mines, and other therapeutic uses of radon in both Europe and America, albeit briefly.

The recent keen interest in exposures of populations to radon and daughters, indoors and out, is taken up for completeness.

American work and U.S. government support were quite significant in the post-World-War-II era. However, the field has not been an American monopoly compared to some of the areas that arose *de novo* during the MED days and which are reviewed in other chapters.

I. Introduction

This chapter brings us into a facet of the toxicology of radioactive materials that is ancient compared to the time standards of most of the subjects in this book, complex and frustrating even to this day, yet of undeniable practical importance. The majority of the human lung cancers recorded as caused by occupational exposure to ionizing radiation have arisen in miners working where uranium was present as the primary or a significant mineral, or where the decay products of uranium and radium were carried into the working environment by water seepage or slow diffusion through porous rock. This is true even when uranium was not the mineral being sought, as was true for several hundred years.^(a)

Even the best uranium ores are far too low in content to pose any toxic hazards from their uranium content per se; nor is the external radiation dose significant ordinarily. It is the decay products of uranium that are the culprits. A glance at the uranium and radium decay series in figure 3.1 and in table 4.3 (chapter 4) should suffice for orientation. Natural uranium has a very long half-life. The first decay product of possible pertinence to the uranium miner is ^{226}Ra . But this has a half-life of 1,602 years and, as the classic story of the Curies testifies, is not easily separated from its ores. However, the next decay product, ^{222}Ra , not only has a short half-life but is a noble gas of very low chemical reactivity. It can leave the ore body or the already mined ore and enter the surroundings. This may occur either directly into the air or by release from solution if it was formed in contact with water and later exposed to air. Furthermore, the next several decay products have from short to very short half-lives. Hence, a rather considerable amount of energy can be released in relatively short times through this process.

A truncated picture of the series showing the elements of principal significance to uranium mining and related activities is given in figure 3.1.

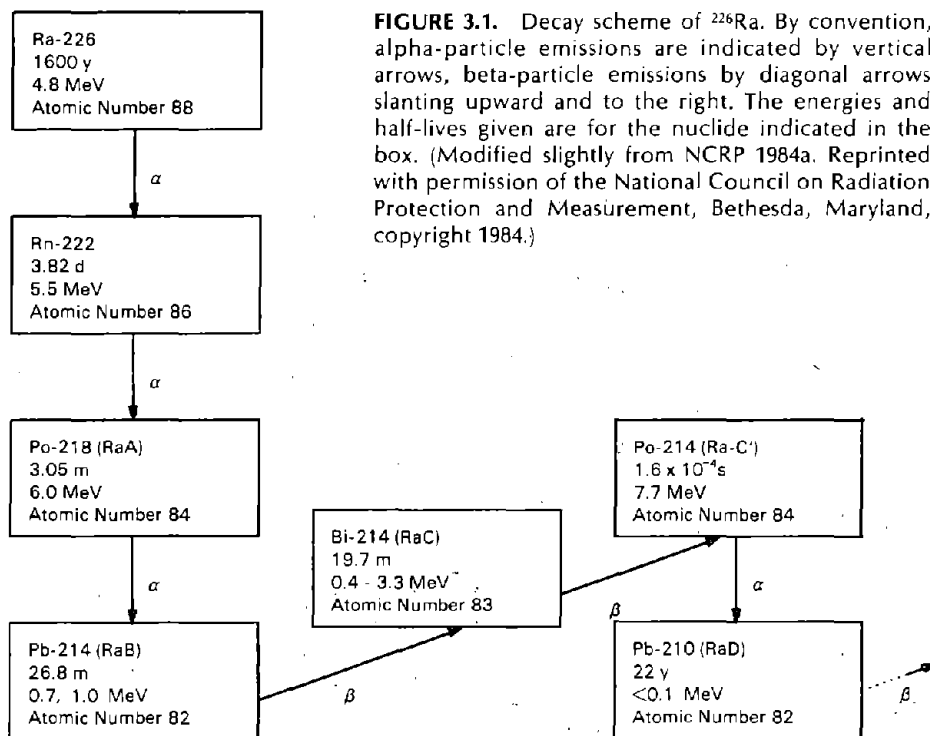
In traveling from ^{222}Rn to ^{210}Pb , over 23 MeV of potential energy are released. It is not all equally effective, as we shall see presently, but it is large nevertheless.

We reiterate. The problem of the uranium miners is not uranium at all. It is radon and its decay products (frequently called "daughter products" in analogy to the time-honored relationship of anything thought of as like a daughter in relation to its source or origin and in the same vein as "daughter cells" in biology).^(b)

Even though the decay products of radon are normally solids at ordinary temperatures, they are produced from radon one by one as single atoms. They will either attach by adsorption or electrostatic forces to ambient dust particles or, if the air is quite clean, exist transiently as free ions. Frequently there are some of both present. Thus, they may remain airborne for appreciable periods.

(a) In terms of sheer antiquity of the exposures, this chapter might be expected to carry the title "First It Was Radon" rather than putting radium first as we did in chapter 1. The reasons we do not put radon in this position are perhaps somewhat arbitrary: (1) the identification and proof of the causative agent was later than in the case of radium, and (2) radon has not occupied the bench-mark position that radium does in our thinking and research because of the many complexities of exposure, dosimetry, and effects, which we shall be examining in this chapter.

(b) Why not sons? Perhaps because the concern is with where these progeny go, and traditionally we worry more about wandering daughters than their brothers.



Radon itself is not very soluble except in fatty tissues. If breathed in, most of it is cleared back out of the blood in only a few minutes. By contrast, the decay products, if inhaled, tend to adhere to lung surfaces, remain there, or be partially absorbed and distributed to other tissues. Thus, radon itself is biologically less important than its decay products.

It is easy to see how, with such short-lived materials, conditions of exposure such as dustiness of the atmosphere, length of residence of the radon and progeny in the mine air, and the physiology of the host, among other things, make for great complexity in determining the true exposures and predicting biological effects. In sharp contrast to the solid progression from cause to effect seen with radium and with many other of the naturally occurring radioactive elements after separation from their ores, the story with radon is fraught with dilemmas and complexities.^(a)

Some of the points that seem obvious now took years to be appreciated and many more years to become established. Furthermore, in comparison with many of the other elements and situations we have been and will be examining

(a) The only one which is worse is thoron and the counterpart problems with the members of the thorium series.

in this book, radon research historically has not been intensive or on a “crash” basis. Excellent people have contributed, some have forged distinguished careers around radon problems. Nevertheless, there has never been a concentrated research effort comparable to that afforded uranium, plutonium, the fission products, fallout, etc., in the efforts of the MED or successor organizations. The ratio of the relatively rapid animal research work to the slow retrospective and prospective epidemiologic studies of human populations is probably the lowest we will encounter. Only in the last three decades toward the end of its long history is the problem receiving really adequate and concentrated attention.

Nevertheless, the amount of literature on radon problems is enormous. As the need for uranium escalated in the late 1940s and thereafter, and the number of mines and miners followed suit, we suddenly realized we faced a first-order occupational hazard with numbers of exposed individuals equal to or greater than any other population exposed occupationally to radioisotopes. There ensued some serious experimental research along with doubled and redoubled attempts to follow the exposed populations. Along with this crescendo of interest came a crescendo of meetings. There were meetings of state officials with the active scientists, ditto with federal officials, with management, state with federal, and some international gatherings. These were important and useful meetings. However, as the pressures for understanding and control mounted, so did the number of meetings until there seemed to be a radon meeting going on somewhere at almost any time. The same data were analyzed and reanalyzed, with frequently only small increments of new information. Thus, the literature grew rapidly. Some of it is in refereed scientific journals; almost all of the early literature is. All of the German and most of the Czechoslovakian literature is in refereed journals and is both good and moderately voluminous. But much of the more recent literature is to be found in enormous tomes, which are unlikely to be shelved in any but the largest university or governmental libraries. So much material had accumulated over such a short period at one point in the post-World-War-II era that one skilled and conscientious reviewer, looking at one aspect only, was driven to declare, “more has been written on this subject than is known about it!”

Now another reviewer is about to add yet another document! He will try to keep it as concise as possible by referencing the easily available literature. He is convinced that even though the field was not of great concern to the MED nor to the Atomic Energy Commission (AEC) in its early years, it is essential that it be reviewed in any book purporting to place the problems of radioactivity and health in historical perspective. Besides, we have learned some things we would have been unlikely to know if it had not been for the problems of radon and radon decay products. Also, it has been realized very recently that environmental, particularly indoor, exposures to radon and progeny may constitute the largest single source of radiation from radionuclides occurring naturally.

II. The Earlier Years in the Mines

A. Mysterious Mountains

Certain mines in Central Europe have been worked for a variety of minerals since about the year 1400. Especially noteworthy are two locations in the Erz Mountains, one in the Schneeberg district of Saxony, Germany, the other in Joachimsthal (in German, Jáchymov in the local language) in the Sudetenland.

This is now part of Czechoslovakia and is on the southern slope of the mountain range some 30 km from Schneeberg.

Miners in both areas lived a markedly shortened life. It was not uncommon for women to have three or more husbands, each of whom succumbed in the prime of life to a disease labeled *Bergkrankheit* (mountain sickness). The symptoms were varied, but usually involved the respiratory tract; then were bathed in superstition. However, some of the very earliest physicians, e.g., Paracelsus (1493–1541) and Agricola (1494–1555) linked the malady to the ores mined and discounted the role of “evil spirits.” Paracelsus labeled the disease at Schneeberg, *mala metallorum*.^(a) In retrospect, we can see that the disease presented was frequently a mixture of silicosis, tuberculosis (which was common), and lung cancer.

There are many interesting and detailed reviews of the Erzgebirge phenomena including biomedical ideas and findings, particularly in the German literature. Probably the most detailed presentation in English appears as part of the chapter on “Cancers of the Respiratory System” in the 1942 edition of William C. Hueper’s monumental volume, *Occupational Tumors and Allied Diseases* (Hueper 1942). The interested reader will find this review of both historical and technological aspects most rewarding.

We will return to these populations in subsequent sections.

B. Identification of Lung Cancer

In 1879, two German investigators, Härtung and Hesse, showed that a majority of the Schneeberg deaths were due to malignant tumors of the lung.^(b)

As recounted in many places (Hueper 1942; Stewart and Simpson 1964; and others), the work of Härtung and Hesse was followed by ample confirming evidence.

Nevertheless, identification and acceptance of the role of lung cancer hardly represented an avalanche. For example, at Joachimsthal (Jachymov) 30 km away, it was *forty-seven years* before evidence of lung cancer in those miners was published. It seems most unlikely that this was due to inattention.^(c) Härtung and Hesse made inquiry in 1879 to officials of the Joachimsthal mines as to whether or not any of the miners there had lung tumors similar to those they were seeing in Schneeberg. After all, the death rate was similarly high, and the disease descriptions seemed much alike. The answer, however, was negative. The Czech authorities stated that not only was there not any *similar* cancer, there was “no cancer of the lung at all at Joachimsthal.” Another inquiry

(a) The Renaissance physicians were quite adept at linking occupational diseases to substances and activities in the workplace. They were, of course, not as adept at mechanisms or true causation. For one recent and moderately short summary with references see Stannard (1980).

(b) Hueper (1942) points out that the correct histological identification of the tumor had to wait until 1926. Since silicosis coexisted with cancer, it seems likely that more than one cell type existed in tumors from these mixed exposures. Hence, lack of accurate identification of the histological type is not surprising. The fact that it was lung cancer was not disputed seriously.

(c) It is true that in these years the enormous health problems of the day were the infectious diseases. Health authorities might be forgiven some lack of full-time devotion to a few miners in a small mountain village, but not the events that we will see transpired later.

decades later, in 1920, still brought an official denial that any instances of pulmonary malignancy had appeared in the Joachimsthal miners. It was not until 1926^(a) that Löwy, a well-known and respected figure in Prague, reported the first two cases of lung cancer from Joachimsthal. (As we will see in section III, this was nailed down by a series of later reports, which continued until 1938.)

We can be sure that the international boundary along the Erzgebirge did not prevent the occurrence of lung cancer on the south side of the mountains for forty-seven years! The conditions, even the levels of exposure were far too similar. The real difference must lie primarily in the reporting.^(b) We can only speculate on the real reasons. The records cannot show what was *not* written down. It is hard to avoid the conclusion that either someone or some organization of the day was not willing to let lung cancer be put down as the cause of death for an unknown but significant number of Joachimsthal miners, or there was not much attention directed to the problem. Hereby we encounter one of the many obstacles that bedevil retrospective epidemiologic research: the reliability of the official record. We will meet this and related problems as we progress through this saga. Much effort was expended in later years to piece together the fragmentary records of the earlier cases.

C. Forays at Causation

The earliest ideas on causation of the *Bergkrankheit* included the metals: bismuth, nickel, and arsenic and the components of cobalt blue pigments. Each of these was called into question only to be eliminated because other mines and factories having these did not have the same health problems. For a while, as genetics began to be understood, a constitutional genetic defect in the populations was suggested. This was eliminated because the problem was limited to miners and laboratory workers exposed to the uranium ores. It did not even extend to miners in populations of other districts: similar genetically (i.e., by virtue of pedigree) but in mines with different ores. The fungi and other flora that grew plentifully in the wet mines were imputed but were eliminated by both experimental work with animals and clinical evidence.^(c) They tried everything, even feeding mud from the mines to animals along with the fungi.

Arsenic was harder to eliminate since it was a proven carcinogen. Also, the Schneeberg miners frequently showed a dermatosis of the hands similar to that seen with exposure to arsenicals. However, other miners (e.g., in France) working with high concentrations of arsenic did not yield the same symptom complex as the Erzgebirge miners. Hence, arsenic was eliminated as a *prime* cause. It still is not certain that it was or was not a cofactor. The same story holds for silica and the role of pneumoconiosis.

In 1921, Uhlig, a medical degree candidate working in the office at Schneeberg, suggested that radium and radium emanation might underlie the

(a) This is the date given by Hueper (1942, 1955) for the Löwy announcement. Others, e.g., Pirchan and Šíkl (1932), cite the Löwy paper as 1929 and indicate that one case was a factory worker observed by Dr. Pirchan, the other a miner. The published paper is dated 1929 (Löwy 1929).

(b) There were some differences in technique, e.g., fluoroscopy versus roentgenograms, but not sufficient to account for 0% versus 50% incidence.

(c) This may not be all wrong, as we will see in a later section.

difference between the Erzgebirge and other areas (Uhlig 1921). (An earlier suggestion along the same lines made in 1913 was not taken seriously.) However, it is a long road from suggestion to proof. An early response was to turn to actual measurements of the radon content of the mine air (e.g., Ludewig and Lorenser 1924). It was definitely elevated in both Joachimsthal and Schneeberg. Furthermore, certain areas that had become known as "death shafts" because of the unusually high occurrence of lung cancer in men who worked in them were found to have especially high concentrations of radioactivity. Furthermore, there were the facts that epidemics of the disease seemed to follow the trails of workers present when a new especially rich ore vein was opened, and drillers and hewers were the most frequently affected class of workers at Schneeberg. These men are the first to come in contact with newly fallen ore and newly opened stopes. Finally, mines in the Johann Georgenstadt district, which had characteristically low incidence of the disease, had relatively low contents of radioactivity in air and water.

Another step toward establishing causation was experimental work. Some very early Russian work (London 1904, cited by Kushneva 1962) indicated toxicity of radon to frogs and white mice. The experiments were acute, and the effects measured appeared largely in peripheral blood. (These may well be the earliest experiments with radon in animals.) Probably the first animal experiment undertaken directly in response to the high incidence of lung cancer among the European miners was that of Jansen and Schultzer (1926), cited by Morken (1955c). This was followed by many experiments from Rajewsky's Institute in Frankfurt, e.g., Read and Mottram (1939), and many others, which we will review briefly in section VIII of this chapter.

Unfortunately, most of the animal exposures were at quite high levels, and the composition of the aerosol with respect to dust, fraction of equilibrium with the daughters, etc., was not controlled because by and large these factors were not appreciated as being important. Some of the German work (Rajewsky) suggested possible increases of lung cancer in mice (but this was complicated by intercurrent illnesses in both experimental and control animals) and some thickening of the bronchial epithelium in the controls. Most of the work did not show lung or other cancers. The levels of exposure were too high and the observation periods too short.

Except for proving that radon as "radium emanation" could be highly toxic, these early experimental tests with animals did little toward confirming the causation of the lung cancers in the Erzgebirge miners. The best of the studies provided suggestive histological changes, but no more. The most convincing proof for Uhlig's guess was the correlation between cancer incidence and radioactivity measurements in the mines. Yet, the correlation was crude and left many loopholes for those with other ideas.

This is roughly how things stood after a period of about four hundred years, i.e., a good description of the disease, a few ideas on control (to be mentioned later), and a shrewd guess, but no complete proof concerning causation.

III. The Middle Years in the Mines

The "early years" discussed in section II encompassed from approximately the fifteenth century to near the end of the decade of the 1920s. It was obvious that research and clinical observations were reaching a new phase of both activity and understanding in the late 1920s. The next decade was sufficiently different

to warrant consideration as an entity even though the changes were as much attitudinal as scientific. Unfortunately, the prodromal phenomena of World War II truncated sadly some of the most active programs of the 1930s, well before the hostilities themselves began. The war halted all such work in Europe, of course.

The mine populations studied were from the same two locations, Schneeberg and Joachimsthal. Many of the miners had been pensioned off by this time, but remained by and large in their native villages. These "pensioners" contributed much of the information gained in this period. Experimental work increased considerably, and measurements and measuring devices for mine atmospheres received much more attention.

A. Accumulating Information on the Miners

The German work that followed Härtung and Hesse in 1879 continued into 1938. Because of the continued relative isolation of Joachimsthal, most of the work in the 1920s and early 1930s involved the mines at Schneeberg, with some work at other German mines known to have different properties. The basic findings remained about as in the previous period, except that more correlation between radon levels and locations of effect accumulated. Correlations with age, years of employment, and time of exposure were methodically investigated. The clinical course of the disease and its pathology were described in some depth, as nicely summarized by Hueper (1942). It became apparent that there were really at least two diseases coexisting—the silicotic process and carcinoma. These frequently interfered with each other in terms of reliable x-ray diagnosis and interpretation of symptoms. Only post-mortem examination, both gross and microscopic, could supply the clearer picture needed. On the whole, the work at Schneeberg became relatively sophisticated by the standards of the day. The fact that these cancers could have long latent periods became quite apparent.

In contrast to the relative silence from the Czechoslovakian side in the 1920s, the 1930s saw some complete and scholarly reports. The best source for our purposes is the paper by Pirchan and Šikl in the *American Journal of Cancer* (Pirchan and Šikl 1932). The work came from the State Radium Institute at Jachymov and the Czech University at Prague, but it was published in an American journal. Reading between the lines indicates that the authors had their reasons for choosing a foreign journal. There is reference therein to earlier frustrated efforts to bring the matter of lung cancer to the attention of either the mine administration of Jachymov or the national health authorities. Things seemed to change only when Dr. Pirchan became Chief Physician of the Jachymov Radium Institute.

The first work from Czechoslovakia chronicles examination of eighty-three persons and a critical study of nineteen miners who died in the period 1929 to 1930. Post-mortem examinations were made on thirteen, of which nine had lung cancer. All had severe respiratory problems in their later years. Detailed case histories are given along with gross and microscopic pathology. In general, the story resembled Schneeberg's, but the cancer, once started, seemed to progress more rapidly and be more malignant.^(a) Hueper comments on the slower progression of the Schneeberg cancers. There was more dust at Schneeberg. This

(a) For the comparison with Schneeberg, the authors used primarily work by Rostoski, Saupe, and Schmorl (1926).

has led some to postulate that the accompanying greater silicosis and greater blockage of lymphatic vessels slowed the spread of the cancer relative to the Joachimsthal cases.

The work in Czechoslovakia was continued by others during 1933 to 1934 and increased in 1934 to 1935 after the government agreed to provide an indemnity to the relatives of the deceased if an autopsy was permitted: Incidence of lung cancer in the miners was steady at about 50%. (The figure had climbed to 75% to 80% in Schneeberg by this time.)

There was in 1935 an official Czechoslovakian government report that based its conclusions on the regular medical examinations (physical, x-ray, and laryngological) of the miners. It contended that only four lung cancers had occurred over the period 1932 to 1935. They pointed to improved ventilation of the mines as responsible for the low rate, forgetting that three years is very short in relation to the known latent periods for lung cancer. Others analyzed data from the Czechoslovakian Ministry of Health from 1929 to 1938 and found the mortality from lung cancer was far higher (as much as twenty times higher) than that in corresponding populations of Prague and Vienna. Thus, we see a continued tendency on the part of the government to play down the incidence and importance of lung cancer.

In further work in the Czech mines, the influence of age, time of exposure, type of worker affected, etc., were analyzed and documented. Except for problems of science versus officialdom and the inherent difficulty of the work, the Czech studies had become very useful and promising.

By 1932, both Germany and Czechoslovakia had made lung cancer a compensable occupational disease. This helped in tracing workers who might otherwise have lost contact by adding the stipulation of mandatory periodic medical examinations.

Measurements of airborne radioactivity in the mine air and water increased greatly. These helped toward establishment of causation. The work did not make any attempt at the ultimate test, establishment of a dose-response relationship. A summary table taken from Bair (1970) shows the composite figures for cancer incidence in the European mines in the entire pre-World-War-II period, i.e., 1875 to 1939 (table 3.1).

The incidence of lung cancer is indeed startling when seen from this retrospective view.

TABLE 3.1. Lung Cancer in Schneeberg and Joachimsthal Miners

Location	Period of Study	Number of Miners	Number of Miner Deaths Studied	Number Having Lung Cancer	Percent Lung Cancer
Schneeberg	1875-1912		665*	276	41.5
	1922-1925	154	21	13	61.9
		353†		2	
	1936-1939	70	6	5	83
Joachimsthal	1928-1938		89	43	48.3

* 119 died of other lung diseases.

† Factory workers and residents of surrounding county.

Source: Modified slightly from Bair 1970.

B. Closing in on Radon

The work of Pirchan and Šikl (1932) already discussed and of Šikl (1930) seems to be generally considered a landmark in pointing to the radioactivity of the mine and laboratory air as a principal causative factor for the disease of the miners. This occurs despite the fact that the idea was suggested earlier for Schneeberg by Uhlig (1921) and by Ludewig and Lorensen (1924). Like all such matters, the progression from suggestion to general acceptance was slow and tortuous. Perhaps the Pirchan and Šikl work is most often cited because it is very complete and very well documented. Also, it is in English!

Attribution to the various metals, particularly cobalt and arsenic, hung on for many years but was gradually moved from primary cause to secondary cause to possible cofactor status. The coexistence of silicosis was almost always a complicating factor in the miners at Schneeberg. As detailed by Hueper, the introduction of pneumatic drilling, which increased the dustiness of the air, led to the idea that the later neoplasms resulted from *radium* attached to silica particles. It was proposed that the silica started an inflammatory process, which was "activated" to a malignancy by the radioactivity from the radium. The argument against radon was that the period between shifts in the mines (about seventeen hours) allowed for complete removal of the radon from the body. This was backed up by laboratory work which showed that all radon inhaled was removed in seven hours. Further, measurements of tissue radioactivity in autopsy material and after animal exposures showed that very small amounts of radioactivity remained, and what was present appeared to be from radium.

Even the idea for a role of radioactivity from radium was given a serious setback when the amounts of radium found were compared to what Flinn (see chapter 1) stated was a hazardous amount of radium (isotope not specified). Flinn's figure was 1.5×10^{-6} g radium equivalent, while the amounts found in the tissues from miners were 1.5×10^{-8} g radium equivalent in one estimate, 1.5×10^{-12} g in another, less than 10^{-12} in still another (Rajewsky 1939). The conclusion was that the radioactivity was too low to play an important role. Tschelnitz (e.g., 1935) was a strong advocate of the innocuousness of the radioactive component of the inhaled air (Heuper 1942).

Others did not share the negative attitude of Tschelnitz. Their views were based on the extent of the cumulative exposure to radon, that over ten years might be equivalent to 15.5 to 31 mg of radium. In addition:

1. It was shown that dust inhalation and silicosis were not a necessary condition for malignancy, at least not at Joachimsthal.
2. Blood changes seen in the miners and in experimental animals were reminiscent of radiation-induced changes in the early highest dosage groups of the radium dial painters and in animals receiving x-ray doses. The correlation was not striking, however, nor was there any quantitation.
3. Correlation of radon content of specific work areas and development of the pulmonary syndrome seemed real. This was the strongest link to the uranium ore and radioactive materials. Correlations between the opening of rich new veins and of working in certain shafts known to have richer uranium ore than others and the incidence of lung cancer were quite positive.
4. Lung carcinoma occurred in laboratory employees engaged in extraction and purification of the radioactive substances from the ores. Very little dust or silicosis was present in these cases, but the radioactivity was present.

Reasonably good, though cumbersome methods for measurement of radon in mine, laboratory, and industrial air were developed in Europe during the years under discussion. Ludewig and Lorensen are credited with the critical measurements at Schneeberg, Böhme (1936) with those at Joachimsthal.

A summary of their measurements, converted from the Mache units of the day to curies^(a) by Evans and Goodman (1940) is given in table 3.2.^(b)

Identification of the mines and shafts in table 3.2 must be left to the perusal of the original literature, except to state that the "Turkschacht," which had some of the highest readings, was among the more notorious locations for lung cancer cases. Note also the large range in the values. This does not mean sloppy technique. It reflects the sometimes large differences in radioactivity at different locations in the same mine. This is related to the degree of ventilation and location with respect to the highest grade ore.

While a direct cause-effect relationship remained somewhat tentative, more and more investigators became convinced radon and airborne radioactivity were the primary causative agents for the lung cancers. Those remaining unconvinced were influenced in part by the failure to produce the lesions in experimental animals and by the low radioactivity of the tissues of deceased miners.

TABLE 3.2. Summary of Published Data on the Radon Content of the Air in Various Mines of the Schneeberg and Jachymov Districts

Mine	No. of Samples	Radon Concentrations per Liter of Air	
		Range	Average
		10^{-11} Ci	10^{-11} Ci
<i>Schneeberg (1923)</i>			
Weisser Hirsch	9	60-320	190
Türkschacht	5	40-1800	550
Neujahrsschacht	8	120-220	160
Siebenschlehen	6	200-870	560
Beustschacht	7	70-180	110
<i>Jachymov (1924-25)</i>			
Einigkeitsschacht	6	30-180	80
Wernerschacht	6	230-880	500
Average of all individual samples	47		290*

* Because of the high values observed at a few points in the mines, the arithmetic average of all individual samples is greater than the median value, which is 180×10^{-11} curies per liter.

Source: Reset from Evans and Goodman 1940. Reprinted with permission of the American Occupational Medical Association, Arlington Heights, Illinois, copyright 1940.

(a) 1 Mache unit = 3.64×10^{-10} Ci/l = 3.64 Emans/l = 364 pCi/l.

(b) Note that these particular measurements were done in the 1920s and thus preceded some of the biomedical correlations we are reviewing here. Many more measurements were reported in the 1930s by the German investigators.

Radon measurements were, of course, being done also in the Western Hemisphere. Some were part of the study of radium patients and workers (see chapter 1). Many were accessory to the radium emanation facilities for production of radon seeds for use in radiology. Some were directed toward factory workrooms and involved thoron, as well as radium and radon (Evans and Goodman 1940). Some were done on breath samples from members of the Armed Forces working in the presence of large arrays of luminous dials painted with paint containing radium (Evans, personal communication 1981). In most cases, the samples were collected in evacuated flasks and, before World War II, sent for analysis to one of the major laboratories. In the United States, these were primarily the National Bureau of Standards (NBS) and Massachusetts Institute of Technology (MIT).

The early measuring devices were large (3-l) ionization chambers. Special precautions were needed to purify the gases used for sweeping the radon sample into the chamber, since for high sensitivity, as low backgrounds as feasible were necessary for the measurements. A description of a typical apparatus for radon, radium, and thoron is to be found in Evans (1935).

Thus, the research during the period 1929 to 1940 moved a considerable distance toward understanding what was going on. There were many who were convinced that radon was the causative agent. There were still problems, however, particularly as the field of radiation dosimetry matured. The calculated doses to whole lung seemed too small to produce the effects seen in comparison to radium doses, which were unfolding in parallel, and to external radiation doses associated with carcinogenesis. There either had to be another factor, or there was some mistake. As we will see in section IV C, the problem was that they *measured only radon and thought only radon*. In what might now be labeled male chauvinistic fashion, they did not focus on the daughters or give them their due!

C. The First Standard

Most of our discussion of exposure and intake standards for radioactive materials is being reserved for chapter 16. The development of standards for radon, and later radon plus its daughter products, is so intimately entwined with the development of ideas and progression of the research that we must make an exception and discuss standards briefly here along with the rest of the story.

In 1941, the first two authoritative standards for radioisotopes in the body were developed. The first was for ^{226}Ra , as will be detailed in chapter 16. The second was for radon. It was derived almost entirely from the work of Evans and Goodman (1940), although it was officially promulgated as a recommendation of the U.S. X-Ray and Radiation Protection Committee of which Evans was a member (NBS 1941).

An examination of data in many different situations led to the conclusion that an average radon concentration in the Schneeberg and Jachymov mines might be taken as 2.9×10^{-9} Ci/l. In round numbers, it was concluded that prolonged inhalation of an atmosphere containing radon at $\sim 10^{-9}$ Ci/l (1,000 pCi/l) could be considered associated with an increase in lung cancer in the miners. Keeping in mind differences in individual radiosensitivity and in the absence of a true dose-response relationship, a factor of one hundred was introduced for safety.

Thus, it was concluded that a safe level for the radon content of the air in plant, laboratory, or office was 10^{-11} Ci/l (in the terms we now use, this is 10 pCi/l).^(a)

While not quite as rock solid as the limiting radium body content figure proposed at the same time, it will be clear by the end of this chapter that this recommendation for radon is close to what we accept currently—except for the complications of the role of the daughter products. But there were to be many intermediate steps—some of them acrimonious hassles of as much political as scientific content.

IV. The Later Years in the Mines and Mills

The period we now enter extends from approximately 1942 to the cutoff point for this chapter—approximately 1984. We add the uranium mills since they became a factor of some significance in these years. However, we will focus still on occupational exposure and save the population and environmental counterparts for separate discussion.

A. The World-War-II Years

The years of World War II were a quiet era for radon research. In Europe no real research was reported. In the Western Hemisphere, measurements needed to be made for radon exhalation by those carrying radium body burdens (chapter 1). Further work was done on radon exhalation from armed services personnel, and, of course, the medical calibrations had to continue.

The radon measurements in the United States continued to be done largely at the NBS and at MIT. However, in perusing old files, this author ran onto a letter signed by Dr. (Maj.) H. L. Friedell (whom we met in the preface to this book) authorizing analyses of radon by the Rochester Project on samples submitted by the University of Chicago (Friedell 1944). This was preceded by a letter to J. J. Nickson in Chicago from W. F. Bale at Rochester that stated the probable error of the method and indicated that it was not sensitive enough to determine radium content of the normal human body by expired breath measurements. The letter does not state what the samples were or for what purpose (Bale 1944). They were not numerous.^(b)

The draft manuscript copy of the book prepared by Dr. Friedell (1981) and very kindly provided to this author by him makes no mention of radon work anywhere in the Manhattan District Laboratories. Obviously it was a low-key subject.

There was one exception, however—a major one. Dr. Egon Lorenz at the National Cancer Institute (NCI) in Bethesda, Maryland, was asked by the Met Lab to carry out a large and relatively long-term experiment on the carcinogenesis in mice of a graded series of relatively low levels of x-irradiation.

(a) This standard was not intended to be applied to the mines. The Europeans were totally involved with the war. In the Western Hemisphere, there were not yet enough uranium mines *per se* to worry about exposure standards. Uranium mining in the United States had hardly begun. The standard was intended for laboratories, factory work rooms, or offices in installations handling radium, producing radon seeds, and the like.

(b) It is the author's conclusion that the samples involved workers at the Eldorado Radium refinery across Lake Ontario from Rochester at Port Hope, Ontario (Hurst 1978).

Perhaps because of his past interests in radioisotopes, including a review of the Schneeberg and Joachimsthal cases (Lorenz 1944), Dr. Lorenz also studied short- and long-term effects of radon. His primary focus was a comparison of the effectiveness of alpha particles (high-linear-energy-transfer [LET] radiation), with photon radiation such as x rays (low LET) in a higher vertebrate.

The radon was given by intravenous injection (not by *inhalation*) of a solution of radon in *equilibrium with its decay products*. Doses were high (0.013 to 0.017 mCi/g). Acute toxicity was compared with x-irradiation doses of 480 to 645 roentgens. (When converted to energy absorption, the RaC' alpha particles, considered the primary source, contributed from 33,800 to 44,200 erg/g, while the calculated x-ray doses gave 44,600 to 60,000 erg/g.) The LD₅₀ for thirty days in the animals receiving the radon solution was about 1.42 times lower than that for the x rays (Hollcroft and Lorenz 1951). This was in the right direction in view of the relative biological effectiveness factors for alpha particles, which were emerging from Met Lab work with isolated cells and organisms. However, it was in no way comparable to the large difference in effectiveness seen in single-celled systems.

This discrepancy led the Lorenz group into a careful study of how the decay products of radon were distributed in the animal by performance of a fairly extensive tissue distribution experiment involving about three hundred mice. The short-lived decay products were found to be distributed very unevenly among organs (they measured twelve entities) and so were the calculated doses. Kidney, intestine, and blood were far ahead in contribution of ergs per total tissue in a 25-g mouse. The total dose calculated from all of these separate analyses was only 3% below the expected dose—a good testimony to the technique.

When tissue weights were taken into account, most tissues got about the average radiation dose, except for kidney, which was about fourteen times higher than the average.

Lorenz had to admit that the outcome of the LD₅₀ comparison was difficult to understand but did not remark upon the possible role of the effects of daughter products. Nevertheless, this was beautiful pioneering work, and the first careful study this author knows of where the behavior of each decay product and the sum of RaC and C' was measured and its contribution to tissue dose spelled out. Thus it is a landmark. It introduced the whole new era of considering the contributions of the decay products formed in the body after radon inhalation.^(a) It correctly showed that radon itself contributes only about 2% of the total dose from an equilibrium mixture and that the RaC + C' contribution predominates.

A second report from the Lorenz group (Hollcroft et al. 1955) followed up on the high dose to kidney noted earlier. A unique alteration of the kidney cortex occurred. It was somewhat similar to that being noted at about the same time by Casarett (1952),^(b) from the passage of ²¹⁰Po through rat kidney. It differed from the nephrosclerosis seen after x rays. This work went to over two hundred days and gave an opportunity for more long-term effects to show. But a small serial sacrifice experiment failed to demonstrate any preneoplastic or neoplastic changes.

(a) Others had indicated awareness of the problem, but this was the first quantitative evaluation so far as this author knows.

(b) This radon work was actually done slightly postwar, but it follows the Met Lab work so logically that we discuss it here. The Casarett work was done during the war, but reported early postwar (see chapter 4).

The work on radon from Lorenz's laboratory is obviously a milestone by focusing on the dosimetry and daughters. While it had only indirect bearing on the uranium miner saga since the route of entry was intravenous, it represents much tedious measurement and some original thinking. As the primary contribution to radon research from the MED days, we can be happy it is of such high quality.^(a) Lorenz calculated radiation doses to lung and concluded that they were insufficient to account for lung cancers in either animals or man.

About the only other event in the radon field during World War II worth mentioning, in addition to the necessary routine measurements, was tinkering with the maximum allowable concentrations by factors of five to ten. These occurred in Canada and the United Kingdom as described by Stewart and Simpson (1964).

B. New Populations to Study

1. Miners

Uranium ore was mined from the late nineteenth century on in the western United States for the extraction of radium,^(b) for use of the uranium as a coloring agent in bottles and ceramics, and during the 1920s and 1930s, for preparation of vanadium. This continued into the 1940s.^(c) During World War II, there was a gradual shift toward use of the ore for nuclear energy. Mines that had been worked primarily for vanadium ore by the U.S. Vanadium Corporation and the Vanadium Corporation of America were found to contain promising, though not exceptionally rich, uranium ores. (Many of the best veins had already been depleted for the production of radium.)^(d) Contracts were let in 1942 between the MED and these and other corporations for production of uranium ore and compounds from both the reopened mines and the tailings and sludges from the vanadium process, which contained uranium and radium in various amounts.

It seemed unlikely, however, to the planners in Washington that these sources could supply sufficient uranium for even the first phase of either the electromagnetic or the gaseous diffusion processes. The OSRD^(e) turned to collaboration with Canada for opening up deposits at Big Bear Lake in northern Ontario through the Eldorado Gold Mines, Ltd. They had supplied uranium ore

(a) Undoubtedly, other good work was done during the war years, both in the United States and abroad. However, we must hew closely to our charter for this book.

(b) There was a radium extraction plant (Radium Company of Colorado) in Denver from the turn of the century until 1924, for example.

(c) An interesting account of all of these operations can be read in the book by Kathleen Bruyn, *Uranium Country* (1955).

(d) It is often stated that Madame Curie used carnotite ore from the United States in her radium work before the far richer ores from the Belgian Congo took over. Evidently, Schneeberg and Joachimsthal were supplying rather low-grade ore. A booklet issued by the Union Carbide Corporation (1952 et seq.) is quite positive on the role of U.S. ores in Curie's work. Others are not so certain. The Colorado ore also got to the Standard Chemical Company processing plant in Canonsburg, Pennsylvania, and it is reputed that they made a gift of radium to Madame Curie for use as a standard in her later work. In any event, uranium mining in the Colorado Plateau was not a completely new phenomenon at the time we are now considering.

(e) Office of Scientific Research and Development, the original organization for World War II Scientific Planning and contractual support.

for some years for preparation of radium at a plant at Port Hope on the shores of Lake Ontario. Arranging to get ore from Canada, without breaches of security, took a bit of doing, but it came about.

Meanwhile, a source of overwhelmingly superior uranium ore from the Belgian Congo was somehow overlooked, albeit temporarily.^(a) The Belgian combine "Union Minière du Haut Katanga," which controlled the African Metals Corporation, had, through the foresight of Edward Sengier, its ranking officer, brought twelve hundred tons of high-grade uranium ore to the United States in 1942, "to keep it out of enemy hands." (How did he know the Americans would need it?) It was stored on Staten Island in New York Harbor. There were, in addition, about three thousand tons of equally high-grade ore already above ground in the Belgian Congo, and arrangements were made to buy it. Most of the shipments of this ore, which could masquerade as ballast for westward-traveling freighters, reached North America despite the hazards of the German U-boat campaign.

By the end of 1944, the U.S. Army had about six thousand tons of uranium oxide; two-thirds of it from the Congo ore, one-sixth from Canadian pitchblende, one-seventh from the Colorado Plateau, and the balance from miscellaneous sources such as tailings.^(b,c)

The activity just described was the beginning of burgeoning uranium mining activities in the Colorado Plateau area of the United States and in northern Canada. As domestic demand for uranium grew, the number of mines grew to over twenty-five hundred in the Colorado Plateau alone by the mid-1950s. Some were large operations, such as the former vanadium mines. Some were one- or two-man operations.

As a result, there were new and retreaded populations to study. Indeed, the total is now seven. Besides the U.S. and Canadian uranium miners, the active population of Czechoslovakian uranium miners was studied intensively. They did their mining in the period 1948 through 1957.

Quite obviously, with so much attention being given to radon, many measurements of radon activity were made in a variety of mines not being worked for uranium. Many other hard-rock mines were found to have from significant to quite high concentrations of radon and radon daughters. This led to a study of quite disparate groups in many countries.^(d) These include:

1. lead and zinc miners in Zinkgruven, Sweden
2. iron miners in Kiruna and Malmberget, Sweden

(a) This was the ore that had preempted those of the Colorado Plateau and even those of Schneeberg and Jáchymov and had caused the former to shift to vanadium extraction.

(b) A more complete history of these phases of the OSRD, MED, and other efforts can be found in the first volume of the official history of the U.S. Atomic Energy Commission (Hewlett and Anderson 1962).

(c) It is hard to resist the view that the foresight of Edgar Sengier and his business acumen (he did plan to sell the ore) aided the MED effort very significantly. We were short of miners, many of the mines were filled with water and took months to get back into operation, and it was in toto a slow process. Sengier deserves more than perfunctory recognition. For further comments on Sir Edward's contributions, see the chapter, "A Thousand Years of Regrets," in Lewis Strauss's book cited in Appendix B.

(d) The groups making epidemiologic units are U.S., Canadian, and Czechoslovakian uranium miners; Swedish and British iron miners; Swedish lead and zinc miners; and Newfoundland fluorspar miners (section VI).

3. fluorspar miners in Newfoundland
4. underground iron miners in Britain and France
5. base metal and hard-rock miners in the United States
6. gold miners in South Africa
7. manganese miners in the USSR.

In all but the last two cases, excess incidence of lung cancer has been reported, but definite linkage to radon exposure was quite uncertain in some of the populations. However, the epidemiologic evidence became strong in the U.S. and Czechoslovakian studies, very suggestive but subject to more uncertainties in the Swedish miners, Canadian uranium miners, and Newfoundland fluorspar miners.

The details of these studies are part of a vigorous scientific polemic at present because of the complexities of cigarette smoking and other potential cofactors. We will enter this arena and take up the results of these epidemiologic studies in section VI.

2. Millers and Others

There were many large dumps left over from the prewar radium mining operations. These were reworked for uranium. Also, during the MED days, the uranium ore went for processing to many of the facilities that had been concerned with handling the ore for other purposes, e.g., for extraction of vanadium, radium, etc. Thus, some of the Canadian and high-grade Congo ore went to the Port Hope radium refinery, but not for extraction of radium. The Mallinckrodt Chemical Company plant in St. Louis had the pleasure of trying the tricky ether extraction on an industrial scale. Many American ores went to plants already under government operation for vanadium processing, e.g., Durango and Grand Junction, Colorado; while later high-grade Congo ores went to the Vanadium Corporation of America plant at Canonsburg, Pennsylvania. The Linde company worked on sludges from the U.S. Vanadium Corporation and later low-grade African ores at its plant in Tonawanda, New York, along the Niagara frontier.

Each of these had somewhat different processes to carry out. (Remember the MED was running on several parallel tracks.)^(a) Personnel exposures to radon and its daughters ranged from negligible to significant. Exposure to radium and uranium *per se* as well as radon and its daughters was fairly common.

Many of the buildings used for these operations are now both obsolete and contaminated. Some have been demolished, leaving a contaminated site. Consideration of these has required a significant effort in environmental and laboratory research (chapter 11).

V. Dosimetric Problems

Before we can profitably review, even briefly, the epidemiologic significance of the several populations described above, we must enter upon the problems of dosimetry. These always have been and still are one of the most difficult aspects of the radon saga.

(a) Hewlett and Anderson (1962) review details of locations and processes, and an overview of the several "tracks" can be found in Smyth (1948).

Necessary allusions have been made already to early considerations of lung dose. Obviously, calculations made before the establishment of radiation dose and exposure units (i.e., in 1927) are difficult to interpret in terms of rad or rem (or grays or sieverts), even though some have been translated to modern concentration units (e.g., curies per liter, see table 3.2).

There are three basic problems in the dosimetry of radon and daughters that have occupied researchers and operators alike. These are, simply stated:

1. What role do the daughter products of radon play? How can their contribution to dose be ascertained?
2. What is the "target" tissue—whole lung or some portion thereof?
3. How can one measure a mine atmosphere in terms that bear a quantitative relation to potential radiation dose and thus biological effects?

Detailed analysis of the research and arguments surrounding each of these questions would carry us far beyond the bounds of available space. Let us, however, consider each briefly with emphasis on historical origins of the ideas.

A. The Role of the Daughters

We have already remarked on the stubborn tendency of the early investigators to neglect the daughters. Even after measurement techniques became reliable and relatively simple, it was usually ^{222}Rn that was measured. The decay scheme had been worked out in the early years after the separation of radium. People knew there were daughters, but only the most careful workers went to any real pains to characterize their atmospheres in terms of "free of daughters," "in equilibrium with daughters," etc. As we have already seen, Lorenz's work toward the end of World War II put the finger firmly on the fact that radon itself contributed only a few percent of the dose from an equilibrium mixture.^(a) Yet, investigators were still thinking of daughters formed *in vivo* after inhalation or other mode of entrance. The radon standard of 1941 (see section III C) was in terms of curies of radon gas per liter, and routine measurements hewed closely to that concept.

Then came one of those "quantum jumps" in thinking that we tend to associate more with the physical than with the biological sciences. In the early 1950s, William F. Bale, Professor of Radiation Biology and Biophysics at the University of Rochester, accepted a temporary assignment in Washington with the Division of Biology and Medicine of the AEC. This was in the years when AEC was first beginning to realize it might have some responsibilities for uranium miners.

Evidently Bale was either set to work on the radon problem or set himself to work on it. The result was a document labeled simply "Memorandum to the Files, March 14, 1951: Hazards associated with radon and thoron" (Bale 1951). This completely revolutionized the dosimetry of radon and thoron! It was never published until the twenty-fifth-anniversary volume of *Health Physics* (Bale 1980). Like all such advances, the idea seems so simple we wonder how it could have been missed for so long, but it was. The point can be made best by quoting the author:

In these and other past evaluations of the hazard associated with radon the vital fact seems to have been almost or entirely neglected that the radiation dosage due

(a) There were others, but their fingers were not as firm.

to the disintegration products of radon present in the air under most conditions where radon itself is present conceivably and likely will far exceed the radiation dosage due to radon itself and to disintegration products formed while the radon is in the bronchi. (From Part II of Bale 1951)

The key is the phrase "*present in the air.*" All but the most artificially cleaned air will have dust particles upon which the decay products produced *outside of the body before inhalation* can adhere. If the air is quite clean, the decay products can exist transiently as free ions. Both of these will be inhaled along with the radon and can contribute greatly to the dose to lung. Bale calculated, for example, that the total RaC' energy delivered to the lungs from an inhaled mixture of radon along with 50% of its equilibrium level of daughters would deliver a radiation dose about seventy-six times greater in terms of total alpha-ray energy liberated in the lungs than would be calculated on the basis of simple equilibrium of radon with its daughter products *produced in the lung*.

Major steps in science seldom occur in complete isolation. This was no exception. John Harley, who had been working for some years at the Health and Safety Laboratory of AEC in New York, decided to complete his Ph.D. work and incorporated almost identical ideas to those enunciated by Bale in his memo to the files. They were in his thesis at Rensselaer Polytechnic Institute in Troy, New York. The work was condensed in a paper in *Nucleonics* (Harley 1953) with emphasis on sampling. The abstract reads as follows:

Abstract—Inhalation of radon daughter products can be more hazardous than inhalation of radon itself. A method is described for simple, rapid determination of radon and its daughters for concentrations as low as 5×10^{-15} Ci/l.
(From Harley 1953, 1980)

Since Harley was a frequent visitor as a consultant to the AEC Headquarters, it is presumed that he and Bale discussed their mutual ideas well before Harley completed his thesis. Bale is usually given credit for the idea because his written version was in 1951, while the Harley thesis and publication were later. It is quite likely that this important step forward was indeed a joint one. Since neither man has made any point of establishing priority, we will not attempt to go further into who was primarily responsible. Probably the idea "just grew" in both minds.

When Dr. Bale returned to Rochester from his Washington assignment, he and Jacob Shapiro, his graduate student and later colleague, set about evaluating experimentally the ideas generated in the memorandum to the files. He and Shapiro exposed animals and humans to radon at various fractions of equilibrium with preformed daughters, in quite clean, normal, and very dusty atmospheres. (The dirtiest carrier atmosphere was supplied by a sparking electric motor.) These experiments supported completely the importance of inhalation and retention of preformed daughters (see Bale and Shapiro 1956; Shapiro 1956; and for more detail, Rochester Project Reports by Shapiro and Bale 1953; and by Shapiro 1954).

Two tables, taken from Bale and Shapiro (1956), illustrate the experimental results. Table 3.3 shows average doses from alpha radiation to lungs and tracheae of rats from radon and daughters in different laboratory-created environments.

It is interesting to note that the experiment shows little difference in average dose to lung between normal outdoor air and the "dirtier" air with electric

TABLE 3.3. Average Radiation Doses from Alpha Radiation to Lungs and Tracheae of Rats Breathing Radon Plus Radon Degradation Products at Radon Concentration of 1×10^{-11} Curies/cm³

No. of Exper. Animals	Average wt. (grams)	Measured Average Dosage to Lungs (millirad/hr)	Average Deviation	Measured Average Dose to Tracheal Epithelium	Average Deviation
— Normal outdoor air —					
9	190	0.22	0.07	0.33	0.04
2	184	0.36	0.07		
— Electric spark nuclei —					
2	186	0.25	0.02	0.11	0.02
— Stagnant cleaned air —					
5	197	0.045	0.010		
5	195	0.047	0.018	0.30	0.11
— Stirred cleaned air —					
3	184	0.0015	0.0003	Too low to measure	
Maximum estimated additional dose due to radon gas undergoing radioactive decay in lungs					
All above animals		0.004		0.003	

Source: Reset from Bale and Shapiro 1956.

spark nuclei. There were evidently already enough dust particles present to act as carriers. Also, in the rat, the average dose to lung was much lower in cleaned air, but the dose to tracheal epithelium was almost the same in stagnant cleaned air as in normal outdoor air. By contrast, stirred clean air produced a dramatic lowering of both average dose to lung and average dose to trachea.

Table 3.4 shows some of the information from the dog. Here the average dose to lung was lower, but that to trachea was about the same as in the rat in normal outdoor air, considerably *higher* with electric spark nuclei, in contrast to the findings in the rat.

Bale and Shapiro checked out two human subjects by measuring retention of inhaled radon-daughter products in a chamber. Normal air was compared to artificially cleaned air.

These experiments and others in the quoted references were enough to convince all concerned of the importance of the daughters and also of the importance of the anatomical dimensions of the airways. Thus, the dog trachea was a better surrogate for man than the structures in the rat.

These ideas and their confirmation had their impact on the regulators and others concerned with radiation protection standards. As recounted by Stewart and Simpson, the calculated dose from the same measured pure *radon concentration* when inhaled decay products were added was about two thousand times higher than predicted by Evans and Goodman in 1940; three hundred times that

TABLE 3.4. Average Radiation Doses to the Lungs and Tracheae of Cannulated Dogs Breathing Air at a Level of 1×10^{-11} Curies/Liter Radon in Substantial Equilibrium with Its Daughters Through RaC'

No. of Dogs	Average Millirad/hr to Lung	Average Deviation	Average Millirad/hr to Tracheae	Average Deviation
— Normal outdoor air —				
4	0.038	0.005	0.35	0.10
— Electric spark nuclei —				
9	0.024	0.006	0.62	0.13

Source: Reset from Bale and Shapiro 1956.

predicted by Mitchell's calculations in 1945, which involved equilibrium with the daughters found in vivo; and about ten times the values predicted by Evans in 1950.

Morgan was among the first to suggest altering the allowable exposure level to radon (Morgan 1951; 1954). In the second memo, he utilized the implications of the Bale-Harley bombshell. Naturally, some of the accepted levels that were thought to have comfortable factors of safety now came uncomfortably close to the maximum permissible dose rate. We will have to leave details to those who are now summarizing the history of radiation protection.

B. The Dose to Lung

Even before the change in viewpoint on the role of the daughters, the assessment of radiation dose to the lung had created problems. We have already seen that early calculations of dose using radon alone, even radon plus some of the daughters produced in vivo and "plated out" on the walls of the respiratory tract, were considered too low to account for the effects seen. This is well-summarized in the excellent paper by Stewart and Simpson. The Bale-Shapiro work plus animal studies at the Naval Radiological Defense Laboratory by Cohn, Skow, and Gong (1953) clearly raised the dose, even the average dose to the lung, to levels consistent with the damage seen. In addition, their work showed that the ratio of dose rates averaged over the whole lung to those to the bronchial epithelium could range from about unity when radon and daughters were inhaled in ordinary outdoor air in the rat to about 1:8 in the dog. They chose for man a ratio of bronchial epithelial dose rate to average lung dose of 5 under the stated conditions of exposure.

However, the translation to man has remained a very perplexing issue. The tumors seemed to be associated with the larger bronchi. In general terms, the dose to this region was higher than the lung average, but the quantitative details did not come out closely enough to satisfy those who expected biology to behave like physics.

There were also such complications as: At what depth below the surface of the bronchus do the sensitive (critical) cells lie? What is the role of the mucus

layer and of various factors such as cigarette smoking, dustiness of the air, presence of ore dust, diesel smoke, and so forth?

Meanwhile, Stannard (1958) proposed that the lung should be regarded as a moderately, but not extremely, radiosensitive tissue, e.g., not as radiosensitive as the hematopoietic tissue. This view has held with time, with the possible exception of the effects of plutonium (see chapter 9). It implies that we should not be surprised at effective doses somewhat higher than for phenomena such as leukocyte counts.

The next steps were to focus down on the relationship between absorbed dose and the incidence of carcinoma and between radioisotope concentration in inhaled air and the dose to the critical tissue. The epidemiologic findings were, as always, slow to accumulate. Yet something needed to be done. Furthermore, the dosimetry side of the equation needed solving to put beside the incidence figures when they did become firm.

The basic steps to arrive at the contribution to total dose of each of the daughter products, whether preformed or formed in vivo, and of radon itself, are individually simple. However, in the aggregate, as many a health physicist has discovered, they present a formidable task. Fortunately, the lucid review of the whole procedure by Evans in his paper, "Engineer's Guide to the Elementary Behavior of Radon Daughters," gives all the physical principles, even how to make calculations from samples collected on filter paper. We need to go no further here than refer the reader to this summary (Evans 1969). Actual values of lung dose will be apparent when we consider the epidemiology.

How to apply the information to the biological system was not so directly answered. It has involved an orgy of modeling; necessary, but frustrating. This activity will be considered in the next section.

C. Modeling

Probably some of the earliest lung models were stimulated by the radon problem. Failla (1942) proposed a simple model of the bronchus that was generalized for all radioactive gases of interest in the MED operations. Mitchell (1945) included the contribution of the decay products formed in the bronchus. Evans (1950) calculated doses using a similar model of a large bronchus, an air concentration of 3,000 pCi/l, and seventeen years as the average tumor induction time to get the total dose to the bronchus as 3,000 rem. However, it was the combination of modeling and experimental observations by Chamberlain and Dyson (1956) that elevated modeling to the position in this field that it still maintains.

Two excellent summaries of the dilemmas of radon lung dosimetry and modeling for dosimetry^(a) have been prepared by H. M. Parker. One (Parker 1966) was a research report prepared specifically for the Federal Radiation Council (via the NAS-NRC); the other was a paper presented in a workshop held by the Health Physics Society at Denver in 1968 (Parker 1969). Both give nearly all we need to know about the basis for the special problems of modeling for radon exposure. It is in the first paper that Parker divests himself of the pent-up frustrations almost inevitably associated with the minutiae of this field and quoted earlier in this chapter, "... far more is written about the subject

(a) General lung models will be reviewed in chapters 9 and 16.

than is known about the subject." The Parker papers added to the understanding of the subject.

Two rather typical models for tissue dose from radon and its daughters were detailed at the 1964 Hanford symposium, *Inhaled Particles and Gases*. Altshuler, Nelson, and Kuschner (1964) did calculations on distribution of activity by size for each nuclide, predicted alpha decay in the bronchial regions, did measurements of epithelial thickness, etc. Except for anatomical measurements, the exercise was entirely calculational.

The second is one prepared by Jacobi (1964) from West Germany. This considered ordinary unfiltered air. He concludes that ciliary transport is a critical factor in bringing activity to the upper respiratory tract and that the highest dose should be expected in the secondary to quaternary bronchi.

For both of these, the general pulmonary retention theories of Findeisen (1935) and their modification by Landahl (1950) were employed.

Many other modeling efforts followed, using stylized descriptions of the respiratory tract (e.g., Weibel 1963), diffusion from an air stream flowing through a cylindrical tube (Gormley and Kennedy 1948), and many variations on the model for a typical bronchus. The aerosol physicists played important roles in all of these efforts.

The modeling efforts have proceeded into the environmental field to consider urban air (Fisene and Harley 1974) and general environmental exposures (Harley and Pasternack 1981). It continues to be an active counterpart to the development of effects data from epidemiology (NCRP 1984a).

With variables as numerous as particle-size spectrum, daughter-product spectrum, free-ion versus attached fraction, physiological and anatomical variations, etc., there is room for many models and for many champions to appear favoring one model over another. While many of the modeling efforts have been purely by calculation, some have been accompanied by experimental checks. For example, the advent of special plastics has made possible remarkably detailed casts of human and animal lungs for checking the theoretical morphometry.

In some instances, the modeling seems to have become an end unto itself, with the biology of secondary interest. We will leave more details of modeling for the interested reader to follow in the references at the end of this chapter and the application of modeling to the working level (WL) concept at the end of the next section.

D. The Need for a New Measure—Genesis of the Working Level

The solution of the major dilemma about the role of radon daughters was scientifically satisfying and of major importance; but it also complicated the lives of those who had to measure exposure levels in the mines or around mills or mill-tailing dumps, or to evaluate exposures. The scientific unit of preference was clearly disintegrations per minute per unit of volume or curies per liter, but of what? The original standards were in terms of radon gas. This would no longer do. Yet, expression as so many picocuries per liter of each daughter was complex and time consuming; see for example Evans (1969) and the Tsivoglou method as detailed in his paper at the 1955 Atoms for Peace Conference (Tsivoglou 1956).

The atmosphere in the mines was almost never in full equilibrium with the daughters except in quiet, unused areas. Air movement caused by natural or artificial ventilation, the activities of ore movement, the size and quality of the

mineralized mass, and other factors^(a) could result in fractions of equilibrium from 0.1 to nearly unity.

It was suggested that an average fractional equilibrium of 0.5 might be used. However, measurements showed that this would not be a satisfactory solution. There was too much variation. Something better, yet simpler to manage than determinations of each daughter individually, was needed.

The rapid expansion of uranium mining in the U.S. Colorado Plateau region in the late 1940s and early 1950s led to requests for assistance in evaluating the mines. Among the first to respond were people from the U.S. Public Health Service (USPHS), along with some representatives of the New York and Grand Junction Operations Offices of AEC. Among the former was Mr. Duncan A. Holaday, an industrial hygiene engineer in the Public Health Service who essentially spent the rest of his career with the uranium miners and radon problems. There was little equipment or "know-how" for the first year or so, but by the summer of 1951 Holaday, Howard Ayer, and assistants had begun environmental surveys of the mines. They knew intuitively that it was alpha dose from the two polonium isotopes (see figure 3.1) that most needed to be measured. They took filter paper samples under widely varying conditions. They got help from the mine operators and state health department people. They slowly worked toward a standard set of measurements by taking readings of activity at twenty, sixty, and eighty minutes after cessation of sampling. This work was helped considerably by the assignment in 1952 of Ernest Tsivoglou, who interrupted his doctoral research being sponsored by the Public Health Service to come to the mines. In the winter months, they collared Howard Cousins, who had been assigned to the station at the time to work out a system. The ideas gradually coalesced into something known at the time as the "Cousin Method" (Holaday 1979). However, there was still no generally accepted approach.

Then came the Seven-State Uranium Mining Conference on Health Hazards held in Salt Lake City in February 1955 with 155 attendees. Here the seriousness of the potential health problems was becoming quite apparent, and the need for some operationally useful measure of potential biological damage from a given atmosphere in a given mine became overwhelmingly urgent (Seven-State Conference 1955).^(b)

(a) A useful summary (from Jammet and Pradel 1956) of the results of monitoring in French mines is as follows:

1. The concentrations found in uranium mines are very high and often exceed 10^{-10} c/l, even with substantial ventilation, of the order of 4 and 8 m³/sec.
2. The concentrations depend, not only on the size of the mineralized mass and its uranium content, but also on the nature and compactness of the rock.
3. The use of explosives to break down the ore releases an important fraction of the bound radon as the rock is broken to pieces. In the blast smoke, concentrations of 5×10^{-8} c/l were found.
4. In the unventilated galleries, radon accumulates in very high concentrations, and by diffusion pollutes the other galleries.
5. The water which circulates in the areas where there are lodes dissolves the radon formed in the cracks and releases it on contact with the air as it seeps down and drips in the galleries.
6. Apparently clean galleries contain substantial amounts of radon brought, either by diffusion through the earth, or carried in by the waters.

(b) Proceedings of this conference are difficult to obtain. This author is indebted to Dr. E. Tsivoglou, Atlanta, Georgia, for a complete copy. The conference was chaired by John Z. Bowers, the University of Utah dean (more in chapter 8).

It is said that the conferees were determined to set some sort of standard if at all possible. Two scientific papers offered suggestions. One by Roy Albert from the Division of Biology and Medicine of the AEC offered a suggestion under the rubric, "the thinking has been (that) 100 micromicrocuries per liter is not a bad number for radon in equilibrium with its daughters." Further along, Paul F. Woolrich (USPHS) stated that "ventilation in the working areas should keep radon degradation products at less than 300 $\mu\text{Ci}/\text{l}$ (total daughters)." Neither man was in a position to do more than offer suggestions, since neither the AEC nor the Public Health Service was legally empowered to control exposure in the mines. But the anxious operators fixed upon these numbers. Even though the minutes of the meeting show no formal action, it seems to be generally agreed that the conference members went home with these figures in mind as a tentative standard.^(a)

Actually this had not solved the problem of mixtures that were not in equilibrium, and most of the mine atmospheres were not equilibrium mixtures. It required one more step to devise a unit that would be useful for control of ventilation and rough estimation of hazard. The latent solution was buried in the cogitations of those present.

In the USPHS Publication 494 (Holaday et al. 1957) a very complete and useful set of tolerance calculations for radon and daughters concludes with the following:

Comment - Sufficient biologic data are not available to determine finally a maximum permissible concentration for radon daughter products. It is hoped that studies now in progress will furnish these data. *In the interim, a working level of 1.3×10^5 MeV of potential alpha energy per liter is suggested for radon daughter products (RaA, RaB, and RaC).* This amount of energy will be released by the decay of 100 micromicrocuries of each of these elements through RaC'. On the basis of present information, the level appears to be reasonably safe and not unduly restrictive to mining operations. (Holaday et al. 1957, p. 20; emphasis added)

This is the first appearance in official print of the "working level" concept. It was obviously not its first use informally. Indeed, the enormously useful chronology of uranium mining health protection activities prepared by C. G. Stewart (1971) states that the Industrial Commission of Utah promulgated a regulation a year earlier that "mine air should not exceed 300 pCi/l of radon daughters (1WL)." (Emphasis added.)

Persistent pressure on Duncan Holaday in personal interview failed to elicit an admission that the term "working level" was of his coinage; but neither did it elicit a denial. Probably it was one of those ideas that grew by consensus.

The interview (Holaday 1979) did elicit emphasis on the interim nature of the idea and that it was not in any way to be considered a standard for planning, etc., but only for operators to use to gauge the effectiveness of their controls.

The working level was defined as any combination of radon daughter products that would produce 1.3×10^5 MeV of alpha-particle energy. This derives from the alpha particle contributions of RaA and RaC' since the beta energies of RaB and RaC are of little importance. Besides, they decay shortly (within minutes or hours) to RaC', which then delivers its whopping 7.68 MeV alpha ray. Thus, the figure refers strictly to potential alpha energy and should be worded as "any combination of the short-lived decay products of radon in 1 l of air that will result in the ultimate emission of 1.3×10^5 MeV of alpha-ray energy."

(a) Note that 100 $\mu\text{Ci}/\text{l}$ of radon in equilibrium with its daughter products is roughly equivalent to 300 $\mu\text{Ci}/\text{l}$ of radon daughters expressed as "total daughters."

Table 3.5 summarizes the definition. Note well that the definition holds for any combination of daughters producing that total amount of alpha energy. Note especially that radon is given no weight in defining the working level.

TABLE 3.5. Definition of the "Working Level" (WL) Unit

Nuclide	α -Ray Energy (MeV)	Half-Period	No. of Atoms per 100 pCi	Ultimate α -Ray Energy per Atom (MeV)	Total Ultimate α -Ray Energy (MeV/100 pCi)	Fraction of Total α -Energy
Rn (Rn^{222})	5.49	3.82 days	1.77×10^6	excluded	none	none
RaA (Po^{218})	6.00	3.05 min	977	$6.00 + 7.68$	0.134×10^5	0.10
RaB (Pb^{214})	0	26.8 min	8580	7.68	0.659×10^5	0.52
RaC (Bi^{214})	0	19.7 min	6310	7.68	0.485×10^5	0.38
RaC' (Po^{214})	7.68	10^{-6} min	0.0008	7.68	0.000×10^5	0.00
Total					1.278×10^5	1.00
Call it					1.3×10^5	

Source: Reset from Evans 1969. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1969.

Note: Even though RaB and RaC do not contribute alpha energies themselves, they decay to RaC' and thus add to the total ultimate alpha-ray energy. Also, there are enough more of them in 100 pCi of an equilibrium mixture because of their longer half-period to result in their contributing a major portion (0.90) of the total alpha energy.

The working level idea took well in the United States and Canada.^(a) Soon records were being kept as products of working levels and time, such as working level months (WLM), even in working level years (WLY). An enormous effort was put into instruments that would give more rapid readings than the ponderous filter-paper-sample technique. The merit of calling attention to the original alpha-emitting decay products and the convenience of having only one entity to measure won the working level popularity far beyond its true validity as a unit.

Many authors have pointed out—indeed measured—the radiation dose equivalent to 1 WL under varied conditions. Obviously, the rad dose to pertinent tissues in the respiratory tract associated with 1 WLM will vary with the fraction of equilibrium, altitude, temperature, breathing pattern, etc. The conversion factors of rad/WLM can range from as low as 0.2 to as high as 10. But mine conditions seldom vary as widely as these factors would indicate since other items were included besides fraction of equilibrium. A figure of about 7 rad per WLM with a range ± 5 was used for a while (Stannard 1973), but 0.4 to 0.8 rad = 1 WLM is the average used in the BEIR III report (BEIR III 1980). This figure is subject to a wide range (Morken 1969; Pasternack and Harley 1971).

The reviews of Evans and Parker, already cited, address the usefulness and the problems of the working level concept. The polemic is still going on as seen in a recent report from the National Council on Radiation Protection and Measurements (NCRP 1984a).

A further source of complexity is, of course, the fraction of *unattached* radon decay products. This is not included in the working level calculation. Since

(a) Never mentioned in the reasons for enthusiasm on the part of the operators is the fact that the WL actually allows levels that are a factor of ten higher than the original standard of 10 pCi/l, assuming that a limit of 1 WL was applied.

these are highly reactive, they would "plate out" in the lungs with greater efficiency than atoms attached to a vector aerosol. Should they be measured separately? Mercer (1975) has analyzed the significance of this fraction and presented data for the unattached fractions of radon decay products in over sixty samples of mine air. While some approached 25% for RaA (even 55% in one case) most were small. Indeed, Mercer and Stowe (1971) discouraged routine measurements of the unattached fraction. Yet, there are those who place special significance on this fraction and view its omission from the working level definition and measurements as serious. This is another area where the research is incomplete and the unit insecure.

The interim nature of the USPHS proposal was seriously compromised by adoption of the working level as a *formal standard* by the American Standards Association. They gave it the force of a maximum permissible concentration. Since then regulators have been prone to use not only the WL and the WLM, but cumulative working level months (CWLM) in regulating U.S. and Canadian operations.

The new unit solved some important practical problems; but the problems of dosimetry and radiobiology were obviously not fully solved. Furthermore, in a sense, having the unit seems to have deterred necessary basic research into both the radiobiology and dosimetry necessary to arrive at the true dose associated with a given set of conditions measured in working level month units. Unfortunately, no really attractive substitute for the working level has been worked out except the old laborious calculation for each daughter. As Parker (1966) stated, "the needed radiation parameters will not be known until the relevant biological target has been more clearly specified." While he urged de-emphasizing the working level concept, it has flourished ever since and will probably continue for expression of radon exposures until the true cause-effect, dose-response relationship is worked out. Nearly all expressions of dose to individuals exposed to radon are now couched in terms of the working level. This includes even the United Nations' recent reports (UNSCEAR 1977, 1982) and recent International Commission on Radiological Protection (ICRP) reports on radon (ICRP 1977, 1981).

Thus, the idea born of a practical measurement problem has become almost an official unit. It is doubtful if a unit with such a range of conversion factors could ever become official in the world of scientific standards, but it has come far—too far—from its original interim status.^(a)

(a) A clear indication of the dilemmas we still face and an instance of applying modeling techniques to the working level concept has come from the group at Harvard whose work on inhalation problems we will meet in chapter 9. Desrosiers, Kennedy, and Little (1978) attacked the problem by reasoning from information from experiments using the Syrian Golden hamster expressed in working level year to human exposures. The abstract of this important paper is given below:

Abstract—A detailed morphometric description of the dimensions of airways, the branching patterns, and the epithelial cell frequencies in the respiratory tract of the Syrian golden hamster has been completed. We used these data to construct a mathematical model of the deposition of inhaled particles and their subsequent regional translocation during extracellular lung clearance. The number of disintegrations per year was calculated for ^{218}Po and ^{214}Po in each airway group using reference radioactive atmospheres. Disintegrations were converted to absorbed dose using the depth-dose distribution in a cylindrical tissue annulus for each alpha particle energy. The resulting doses show a significant difference between the types of cells and locations receiving maximum exposure when the model of the hamster lung was

E. Methods of Measurement^(a)

Although general methods for measurements of radioactivity are described in chapter 17 and those intended especially for field application in chapter 18, we should pause briefly to look at those for radon and its daughter products. Fortunately, a recent ICRP report (ICRP 1977) contains a succinct summary. A number of U.S. laboratories were actively engaged.

The techniques fall into four categories: (1) radon concentration, (2) radon daughters, (3) unattached radon daughters, and (4) radon and radium in water. Excerpts and paraphrasing from the subject ICRP report should suffice to illustrate the principles.

1. Radon Concentration

Routine measurements of radon concentrations in mines are usually made by taking samples in the mine for measurements at ground level. The samples are taken in scintillation flasks or evacuated metal containers. Activated charcoal is also used as a sample collector. Sometimes a technique called the two-filter method is used, and in this case measurements in the mine are preferred (ICRP 1977, p. 18).

The two-filter method consists of drawing air through a pipe fitted at both ends with filters for radon daughters. Radon daughters in the incoming air are trapped by the first filter; the daughters trapped by the second filter are those formed during the passage of the radon between the first and second—the radon daughter activity at the second filter is proportional to the radon concentration (ICRP 1977, p. 19).

2. Radon Daughters

All methods involve collecting an air sample on filter paper for a given time at a known flow rate. Variations are in the methods of counting, the times the counts are made, and other details. The Tsivoglou method (see page 22 of ICRP 1977 and Holmgren 1974) measures the individual concentrations of RaA, RaB, and RaC in air.

3. Unattached Radon Daughters

Unattached radon daughters can be separated in the field by collection on a wire screen. Mesh size and sampling velocity must be worked out carefully.

compared to current models of the human respiratory tract. The dose to basal cells in the subsegmental bronchi is 0.4-1.6 rad per working level year (WLY). The mean dose to basal cells is 2-3 rad per WLY. Peripheral basal cells may receive doses approximately equal to doses received by basal cells in the central airways. Moreover, Clara cells in the terminal bronchioles may also receive 2-3 rad per WLY. Since Clara cells have been implicated in hamster lung carcinogenesis, the dose to these differentiated cells may be relevant to inducing tumors. In contrast, models of the human lung suggest that the highest dose to all types of cells is in the higher airways (subsegmental bronchi) and that the cancer-related dose is 3-20 rad per WLY for identical ^{222}Rn -laden atmospheres. Although these results are subject to the limitations inherent in the mathematical modeling of biological phenomena, they indicate that the frequency, and morphology of ^{222}Rn -induced lung cancer in hamsters may not be a straightforward indication of human response when exposures are expressed in WLY. (Desrosiers, Kennedy, and Little 1978).

(a) There is considerably more detail on measurement techniques in the recent special issue of *Health Physics* edited by Nero and Lowder (1983).

4. Radon and Radium in Water

For radon and radium in water, samples are taken at the point of entrance of the water into the mine (*not* from pools, the floor, or other sites where radon loss and/or contamination can occur). The whole bottle of collected water can be placed on a NaI crystal, or the radon can be transferred by the passage of air into a measuring chamber. These determinations are better made away from the mine itself and using conventional laboratory techniques.

VI. The Epidemiologic Studies in the Postwar Era

We have already summarized the new populations exposed occupationally to radon that became available for study in the post-World-War-II era. In this section, we will review briefly the genesis and results of epidemiologic studies as they now stand. Since there are already numerous reviews of the facts and their interpretation, emphasis will be placed here on the historical development of the work, particularly in the United States.

It was once the hope that the miner populations might produce results that could stand beside the ^{226}Ra , ^{228}Ra , and the ^{224}Ra studies described in chapter 1. That hope is fast fading. The conditions of exposure are so varied and so difficult to pin down that despite the best efforts of all concerned, we will probably never have as solid an indication of dose as we do for the radium cases. There is, of course, no residual body burden of the primary nuclides to measure, which throws the burden on in-situ measurements of exposure or assay of the long-term decay products either in the body or excreted. Efforts have been made to use the ^{210}Pb content of bone or its excretion (Bell and Gilliland 1964; Holtzman 1970) or, better, the urinary excretion of ^{210}Po (Sultzner and Hursh 1954; Djurić et al. 1964) to estimate the radiation dose retrospectively. There is clearly enough polonium excreted to measure conveniently in many miners with moderate to high exposures; but the connection to lung dose is a tortuous process.^(a) Another reason we cannot expect much more than we now have is that exposures have been greatly reduced (fortunately) by the institution of control measures. Nevertheless, the subject is of paramount importance in terms of numbers of exposed individuals and incidence of effects. A review is essential to any history of radioactivity and health.

A. The U.S. Uranium Miners

1. Assembling the Data

The study of the U.S. uranium miners has centered, in terms of manpower, in the U.S. Public Health Service, Division of Occupational Health. This Division had assistance from other sectors of the Public Health Service (including the National Institutes of Health) from AEC laboratories (notably the Health and Safety Laboratory in New York and the University of Rochester Atomic Energy Project) plus close collaboration with the states and the mine and mill operators. Geographically it has centered in the Colorado Plateau. The nearest thing to a

(a) Quite recently, European investigators have tried relating the ^{210}Pb content of teeth to exposure to radon and radon daughters (Clemente et al. 1984).

single center for the activity has been Salt Lake City, with Grand Junction an accessory center.

The genesis of the study is best told in the words of Duncan A. Holaday, who had an important part in every technical study, except the purely medical evaluations, and who traversed, personally, a substantial portion of this wild and beautiful area.

The following excerpt from Holaday's review in Volume I of the IAEA symposium is a good way to start:

Early in 1949, after the uranium-mining industry began to expand in the State of Colorado, the Public Health Service advised the Executive Secretary of the Colorado Department of Health that there were potential health hazards associated with the mining of uranium ores. Following a preliminary investigation, the Department of Health, the Industrial Commission, and the Bureau of Mines of the State of Colorado, and several of the larger uranium mining companies, requested the Division of Occupational Health of the United States Public Health Service to conduct a study of the potential health hazards associated with the mining and milling of uranium ores.

In the United States of America legal responsibility for protecting the health of workers is a function of the various states. The role of the Public Health Service in such matters is limited to research, including defining the problem and developing standards and control methods. The application of this knowledge is then a responsibility of the states concerned.

While negotiations with the State of Colorado were underway, limited study of the health problems in the uranium mines located on the Navajo Indian reservation of Arizona was conducted by the U.S. Public Health Service.^(a) This study indicated that the miners were exposed to external radiation, radon and a high silica dust containing an undetermined amount of radioactive elements. Additionally, it appeared that the vanadium and uranium contained in the dust were of toxicologic importance and that the matter of internal radiation due to the inhalation of radioactive dust also should be considered.

Concurrently, a review was made of the European experience and the literature was reviewed for contributory information. It was concluded that the health study should consist of two correlated phases: a medical study and an environmental investigation. Although medical examinations probably would not be immediately productive in uncovering pathologic changes because of the limited exposure period of the uranium miners, it was felt that the examinations should be given to establish rapport with the miners and the mining companies and to obtain baseline data regarding the mining population. Medical examinations of the miners and mill workers were performed during the summers of 1950 and 1951, during which time 1117 persons were examined with essentially negative findings. In 1953, it was decided that medical examinations be given on a triennial basis, with major emphasis on careful follow-up of active and inactive miners. . . . Uranium-producing mills were included in the original study concept. However, when it was determined that the mills were within the purview of the Atomic Energy Commission's regulations, the study was limited to the mining industry. (Holaday and Doyle 1964, references deleted)

From miscellaneous sources in Mr. Holaday's and this author's files, we can present the following:

1. When the PHS Division of Occupational Health was designated to assist Colorado in 1949, they had two survey meters for measuring external

(a) The U.S. Bureau of Mines is also stated to have surveyed mines on the Navajo reservation in early November 1949.

radiation; no equipment or competence for making radon, uranium, or radium measurements; a limited staff and no funds for such a study. One man was assigned by the PHS. Dr. Cleere, Colorado Department of Health, set up an advisory committee to consider uranium mining problems.

2. In December 1949, a grant application from the state of Colorado to the National Cancer Institute brought twenty-five thousand dollars for environmental and medical studies. The radon samples were sent to the National Bureau of Standards for measurement, uranium and radium in atmospheric samples were sent to the Naval Radiological Defense Laboratory, and the Los Alamos Laboratory did urine analyses.
3. In 1950, actual medical field work was started, but this was at the Durango Mill of the Vanadium Corporation of America. Later, workers from other mills were examined, and it was proposed that miners be brought to the mills for examination.
4. In December 1950, it was the consensus of all concerned that exposures to radioactive dust and gas in the mines were high enough to be of real concern. No reports were published, however. Financial help was sought from the AEC.
5. In 1951, the primary medical effort was expended on miners, and a new grant was obtained from the NCI.
6. Also in 1951, environmental measurements in nonuranium hard-rock mines indicated lower but still significant amounts of radioactivity therein.
7. In 1952, the state agencies and mine operators were urged to institute control measures to reduce exposures. AEC was asked for substantial financial help. (They had already loaned equipment from the New York office through Drs. John Harley and Merrill Eisenbud.) The Division of Biology and Medicine of AEC provided twenty-five thousand dollars. This, together with the PHS money, enabled a crew of six men to survey 159 mines during the summer. AEC also started surveys in Commission-leased uranium mines.
8. No medical examinations were done during the 1952 field season. An unpublished interim report of fifty mines and eight mills was prepared within PHS.
9. Medical examinations were resumed in 1953, with primary emphasis on the miners.
10. The epidemiologic phase became the responsibility of the NCI in 1953, leaving the Division of Occupational Health (DOH) primarily responsible for the environmental work.
11. In summer 1953, the Utah State Health Department surveyed all the operating mines in the state. Other states were much less well covered. They reported radon concentrations from 0 to 2,100 pCi/l in the mines, with most of the samples in the 500-pCi/l range.
12. In 1954, the epidemiologic team became a discrete entity. Also, with the help of the Grand Junction Office of AEC, teams were assembled to do a much more sophisticated type of survey. They used x-ray trucks, trailers where examinations could be made and hematology could be done, plus support equipment such as water tanks, generators, etc. Also in 1954, the revised Atomic Energy Act gave AEC control over material once it was removed from the mine.

13. In 1955, Utah issued regulations for control, and the standard for atmospheric concentrations was that referred to in section V of this chapter. Colorado prescribed 100 pCi/l for each of the alpha decay products. Also, better follow-up procedures for the medical study group were established, and a census of all uranium miners was developed. The work for this was carried on largely in 1956.
14. In 1956, both the environmental and medical surveys continued. However, the Bureau of the Budget stated that it did not approve of federal funds being spent on the uranium study, and the work was limited to assisting state agencies on request. AEC presented the first results of surveys of thirty-five Commission-leased mines. They were from two to eighteen times above the working level.
15. In 1957, an extensive medical survey was conducted with the same *dramatis personae*, except that Dr. Victor Archer replaced Dr. Eagan in charge of the medical field work. The census was combined with the medical study. How the negative attitude of the Bureau of the Budget was reversed or circumvented is not set down in any of the materials available to this author. No publications were released.
16. In 1958, it became apparent that four new deaths from lung cancer had occurred in the worker population. Despite this, control of the mine atmospheres was still quite unsatisfactory. None of the state mine inspectors felt they had authority or that the data were convincing enough to require the expensive and awkward controls needed. They did what they could by "education and exhortation."
17. A third general medical survey was conducted in 1960. The data began to be subjected to in-depth analysis.
18. During several meetings in 1961, many company representatives expressed disbelief in the existence of a medical problem, but the reputation of the U.S. Public Health Service never to "cry wolf" and never to have to retract a considered opinion seems to have impressed many.
19. After the "Governors' Conference" in 1961, many areas of some mines were caused to be shut down (Governors' Conference 1961).
20. As a result of Dr. Saccomanno's work at Grand Junction showing the miners' cancer cells were cytologically predominantly of the "oat cell" (i.e., small cell) type, an annual sputum cytology program was instituted about 1961.^(a)
21. Despite niggardly appropriations from Congress, the medical and environmental field work continued through 1963, when the medical phases were severely curtailed. This was partly because the levels of exposure were now reduced and it was a matter of waiting out the latent period for cancer induction, partly because the effort and funds needed to be concentrated on data analysis and environmental surveys.
22. The census/sputum-cytology program was continued into 1964. The number of cancer cases began to increase rapidly.

The laboratories participating have already been named. Personnel waxed and waned since much of the work was done during the summer season by

(a) This characteristic of the cancer cells undoubtedly existed for a time, but the consensus now is that the undifferentiated small cell type is not universal or unique. Saccomanno shares this view (footnote b, page 153).

temporary assignments, and there was the usual shuffling of PHS officers characteristic of a semimilitary organization. Some names need special notice, however. For the medical surveys we should note:

Public Health Service: V. Archer, W. C. Cooper, J. W. Egan, E. Harris, W. C. Hueper, F. E. Lundin, H. Magnuson, R. W. Miller, J. K. Wagoner, and M. R. Zvon.

Others: Grand Junction, Colorado: G. Saccomanno, St. Mary's Hospital and Veterans Administration Hospital. Grants, New Mexico: M. A. Connell, Grants Clinic, Medical Consultant to several companies. University of Rochester School of Medicine and Dentistry: A group led by M. L. Ingram spent one summer doing medical examinations and hematological determinations on miners throughout a large area. Results have not been identified individually.

For the environmental surveys we note especially:

Public Health Service: S. C. Black, R. L. Blanchard, H. Doyle, M. Haij, C. Jensen, H. Kusnetz, P. A. Lawrence, and E. C. Tsivoglou.

Others: AEC: W. F. Bale, G. M. Dunning, M. Eisenbud, and J. Harley. Colorado State University: A. Dahl, K. Schiager, and others.

In addition, a number of personnel from agencies of the states of Colorado, Utah, and New Mexico took active parts.

Ubiquitous to all phases was D. A. Holaday, whom we should regard as "Mr. Radon" for the U.S. efforts.^(a) His review in a 1974 National Institute for Occupational Safety and Health (NIOSH) document (Holaday 1974) gives a clear overview of the efforts and of Holaday's comprehensive grasp of the field.

2. Results of the U.S. Epidemiologic Study

Like all epidemiologic studies, definitive results came slowly. Yet, it must have been apparent even from the early returns, the measured environmental levels, and the experience in Schneeberg and Jachymov, that numerous American underground miners were slated to die of lung cancer.

An early report of the PHS work appeared as two papers in the International Atomic Energy Agency (IAEA) symposium already cited. One concerned non-fatal effects (Archer et al. 1964). This was limited to the respiratory system. The other report gave gross mortality patterns for miners and millers, 1950 through 1962 (Wagoner et al. 1964). There was an increase in mortality in the miner group, but due primarily to accidents. The authors comment, however, that there was a tenfold excess in incidence of respiratory cancer among the miners with long-term underground experience.

There followed an extremely active period in review of the American data. The Federal Radiation Council (FRC) gathered opinions from all quarters on the PHS data and their analysis. This resulted in a preliminary FRC report, which was issued without recommendations. The Joint Committee on Atomic Energy (JCAE) called a series of hearings on the uranium miner problem in 1967 (JCAE 1967). The FRC preliminary report was released for discussion at these hearings. The PHS brought in its most recent data and analyses. There were questions

(a) It is fitting that Mr. Holaday was the first recipient of the distinguished achievement award of the Health Physics Society at its meeting in June 1968.

raised about these,^(a) and an interdepartmental committee was set up to resolve the outstanding questions and come up with recommendations. The FRC reviewed its preliminary report and issued a revised version in September 1967 (FRC 1967).

Because of the growing political overtones in the uranium miner saga (see section VI B), the Federal Radiation Council requested assistance from a blue-ribbon advisory committee of the National Academy of Sciences-National Research Council chaired by Cyril Comar (the first of two such committees) (NAS-NRC 1968). They concluded that the chief problem at the low exposure levels was allocation of workers to categories of exposure. After all, the measurements were only spot checks and were always subject to local conditions. They held that the increased cancer incidence above 400 CWLM was clearly significant and that an increase between 100 and 400 CWLM was not an artifact of the data, although causation was not so clear. They concluded that cigarette smokers were particularly susceptible.

Interim recommendations were made for limiting mine exposures, and plans were made for lowering the levels on a predetermined schedule. However, the schedule had to be changed and delayed. The JCAE called more hearings in 1969 (JCAE 1969).

The interdepartmental committee, which now had the name "The Inter-agency Uranium Mining Radiation Review Group" (IUMRRG), issued a series of reports on all aspects of the problem from health effects to economic factors. Its final report was reproduced in the *Federal Register* in 1971 (*Federal Register* 1971). Also, a second NAS-NRC report was sent to the IUMRRG (NAS-NRC 1971). Nearly everyone with experience in radon problems was called upon to testify or sit on one of the committees.

During the middle of this period of examination and re-examination of the data, Willard Wirtz, then Secretary of Labor, invoked the Walsh-Healy Act and on May 5, 1967, arbitrarily set a level considerably lower than any of those under consideration: 0.3 WL. There was no scientific evidence to support such a drastic decrease, nor was it "reasonably achievable" at the time, but it had to be probed along with the technology. The motivation was undoubtedly the Secretary's desire to protect the miners as fully as possible, impatience with the haggling of the scientists and technical people in general, and an understandable emotional ingredient in the fact the Secretary had lost two family members to cancer. While technically not attainable at the time, the setting of this low level undoubtedly influenced the process of gradually decreasing the official occupational exposure standards with 1 WL accepted in principle by FRC in July 1967.

A moderately complete new report from the Public Health Service was published in 1971 as a joint monograph from the National Institute for Occupational Safety and Health and the National Institute of Environmental Health Sciences (NIEHS) (Lundin, Wagoner, and Archer 1971). This showed a total of 437 deaths compared with 277 expected in white and 72 deaths compared with 90 expected in nonwhite underground miners. Most, but not all, were caused by malignant neoplasms.

There was no question in this report of there being a causal association between lung cancer incidence in the mines and exposure from 400 up

(a) It should be recalled that the uranium miner study was not originally set up as a true epidemiologic effort.

to 1,000 CWLM or more. It was also clear that there was a statistically significant increase between 100 and 400 CWLM contributed substantially, but perhaps not entirely, by radon daughter exposures. Overall, the lung cancer incidence for the period 1950 to 1968 was about six times that of nonminers.

Problems still resided in the studies, however. The significance of exposures at levels below 100 CWLM could not be established with the data in hand. Yet, it was at these lower levels that most interest centered, because of the strong desire to establish firm standards. Also, the role of cigarette smoking was difficult to work out. For a while, it seemed as though no miner who did not smoke got lung cancer. But this seems to have been partly a trick of the data. As explained by Holaday (1979), taking a simple answer to the question, "Do you smoke cigarettes?" was not enough. It needed to be followed by, "How many?" Many of the Navajos smoked almost not at all, but would answer yes to the simple question since having money to buy cigarettes was considered a status symbol. The smoking might amount to one or two cigarettes in town on a Saturday night!^(a) Again, note the problems of record-keeping and importance of an intimate knowledge of the situation at hand for the conduct of retrospective epidemiology. Cross et al. (1974, section 2.4) give a full and readable summary of the activities of this period and their impact on the final standards set. Also in 1974, Holaday produced his summary report for NIOSH (Holaday 1974). We will defer to them for further details.

As of 1981, the U.S. Uranium Miner Study consisted of medical studies of 3,366 white men and 780 nonwhite men (mostly Navajo Indians) who had at least one month of underground employment in 1963 or before. About 43,000 radon daughter measurements were made, mostly between 1951 and 1969, after which levels became too low to continue to figure in the study. Lung cancers are now above expectation in all exposure categories above 60 WLM. Exposures extended from less than 100 to nearly 10,000 WLM (Archer, Wagoner, and Lundin 1973).

A linear relationship between dose in working level months and cancer incidence has been plotted by many, but the true shape of the dose-response curve remains for future work to ascertain. We can expect new summaries in reports now in preparation, but these are not yet history.

The interpretations have been extended to induction rates (UNSCEAR 1977) and to risk estimates (Evans et al. 1981; BEIR III 1980; and others). Any further discussion of these matters would carry us beyond our time and scope.^(b)

It appears that the U.S. epidemiology study is now one of the most complete and secure of all we have. It represents an enormous effort under trying field conditions. While the precision of such results can never be expected to match those of controlled laboratory experiments, they have the advantage of being composed of data on man exposed in "real-world" situations. Also, they show what can be done by dedicated workers on relatively small budgets.

(a) Inquiry to Dr. Saccomanno at the NCRP annual meeting in March 1988 negates the importance of this point. In his experience, most of the miners who smoked were heavy smokers.

(b) Incidentally, in some categories it appears now that cigarette smoking may lower incidence of bronchiolar carcinoma because of the increased thickness of the mucus layer. Also the predominance of small cell types in the lung cancers seems to have disappeared. In fact, other cell types appear to be taking over. It is the opinion of Saccomanno (1981) and Saccomanno et al. (1981) that the types being seen now are so characteristic of cancers induced by cigarette smoking that it may indicate that the new cases are only tenuously connected to radiation exposure.

About the time of the nominal cutoff for this historical review, the field opened wide, as we will see presently.^(a)

B. Why Did it Happen Here?

When it became apparent in the 1960s, and beyond, that the United States would have several hundred cancer deaths among uranium miners, and this despite the well-established experiences in prewar Germany and Czechoslovakia, many officials, agencies, individuals, and organizations indulged in the usual practice of "Monday morning quarterbacking." Special vituperation was vented upon the AEC for not taking a firmer hand, or indeed taking over the situation, early in the 1950s. The stark contrast between protection of uranium miners and that afforded other workers in the atomic energy industry aggravated such thinking.^(b)

Few seem to realize that what was done, as recounted in the previous section, was only following the general pattern of the day of all federal relationships to industry. The states had the responsibility for protection of their workers, and they guarded it jealously. Always the Public Health Service provided advice and information *when asked*, assistance *if specifically requested*; but they never made an attempt to take over or even give the appearance of doing so. Only on federal lands could agencies such as the Bureau of Mines exert control of mining operations.

(a) In 1979, the Colorado School of Mines sponsored a conference/workshop, Lung Cancer Epidemiology, which included updating papers on effects of exposures to low levels of radon and discussion of factors involved in exposure-response relationships (see, for example, Archer 1979). In 1980, a specialist meeting, The Assessment of Radon and Daughter Exposure and Related Biological Effects, was held near Rome, Italy. The proceedings were edited by Clemente et al. and were published in 1982. Several pertinent updates of the subject of this section were included, e.g., Cross et al. (1982); Fisher (1982); and Steinhäusler, Pohl, and Hofmann (1982). In 1981, the Committee on Indoor Pollutants of the Board of Toxicology and Environmental Health Hazards of the U.S. NAS-NRC produced a report that summarized information on dose-response calculations (NAS-NRC 1981). Also in 1981, an international conference was held at the Colorado School of Mines, Golden, Colorado, on radiation hazards in mining. It was sponsored by the American Institute of Mining, Metallurgical, and Petroleum Engineers (Gomez 1981) and contained thirty-six identifiable technical sessions, several planning sessions, and luncheon addresses. The sponsors stated that this was the first international convocation of scientists, engineers, and various health specialists that concentrated on *ongoing research throughout the world*. There was considerable discussion of epidemiology, standards, and methodology. Perspective on the cancer problem is given by Archer (1981).

In the even more recent past, Bair (1986) included much germane discussion on radon problems in his general review of experimental carcinogenesis of the respiratory tract; Whittemore and McMillan (1983), working at Stanford under a PHS grant, reappraised the lung cancer mortality statistics among U.S. uranium miners and suggested a multiplicative function; Cross (1984) produced a complete review of animal data on radon inhalation; and finally, two NCRP reports were issued (NCRP 1984a, b). It is obvious that the subject remains extremely active. The emphasis has shifted, however, to nonoccupational exposure. We will review this new emphasis briefly in a subsequent section of this chapter and in the environmental chapters.

(b) A useful and authoritative review of many of the considerations in this section can be found in testimony presented by Merrill Eisenbud before the Subcommittee on Health and Scientific Research of the U.S. Senate in June 1979 (U.S. Congress 1979).

The Atomic Energy Act gave AEC jurisdiction over many processes and areas which, had the material been for nonnuclear use, would have been completely a states' rights proposition. However, as the historical notes of the previous section show, this jurisdiction did not extend to mining. Before 1954, it did not even go as far back as "material once removed from the ground." Legal counsel of the AEC repeatedly advised the Commission's officers and personnel to refrain from overstepping the statutes, and to stay out of the mines. They were under PHS cognizance if any federal participation was needed!

We have seen that AEC provided funds, equipment, and personnel even if perhaps not in the volume really needed. We have also seen that the federal establishment broadly was loath to give proper financial support when it was most needed—in the early years. We also know that the operators, faced with meeting contracts, were not anxious for a spate of new regulations and increased expenses and delays in production.

Other factors are more or less idiosyncratic to the uranium mining operation. Ventilation was the best answer. But not only did it cost in power and equipment, many of the mines had only portable generators, and long supply lines for fuel were needed. In winter, the necessary ventilation produced blasts of cold outside air, which made the workers want to tie off the inlet pipes. Sometimes they did. Inducing personnel to wear respirators has always been a problem in industrial operations. In the uranium mines, especially the small ones, respirators were a lost cause in the early years. Many of the smaller mines would have had to close since they could not afford the expense of ventilation equipment. At that time, uranium ore was needed urgently, for the "cold war" was blowing hotter than most realized. The AEC was on the horns of a dilemma with regard to reducing the flow of ore versus enforcing controls or trying to do so.

All these factors, plus the continued skepticism of many as to the reality of the problem, resulted in a very long period of what now appears to be culpable inaction, but what was at the time a result of opposing forces and inertia.

There are many who hold that the AEC was all too willing to accept the dictum of their legal counsel and stay away from the uranium miner area, except for lending assistance. The AEC, as will be seen in chapter 12, already had its hands full with the fallout ruckus. Also, any overt intervention might strain relations with the PHS, which clearly had the statutory priority. As an employee of a related division of the PHS during some of the years just prior to the expansion of uranium mining, this author can testify to the sanctity surrounding the PHS relations to the states. Perhaps the AEC could have been more aggressive. Only those in the seats of responsibility at the time can testify.

The real tragedy of the U.S. uranium miner saga is not that the AEC did or did not push people around, or even that the PHS and the federal Treasury were too parsimonious. It is that the lessons of Joachimsthal and Schneeberg had to be learned all over again. As soon as the radon levels were found to be equivalent to those in the European mines, the outcome was apparent, unless something was done and done quickly. Instead, we waited to prove that radon daughters could kill Americans as well as Europeans.

Does this mean that American science was callously disregarding the human suffering involved? Anyone who follows the tortuous process of establishing a scientific fact knows the answer to this question is negative. There were lingering doubts even about the European studies. The general health of the European miners, even in the 1920s and 1930s, was poor by Western standards of the late 1940s. Cofactors had not been eliminated from consideration, and they were

clearly potentially different in the two situations. Indeed, this possible complexity is not yet fully eliminated from consideration, nor will it ever be until we know cancer biology much more fully.^(a)

As Cross et al. (1974) point out, in retrospect, we had the data to set a standard of 6 WLM by the early 1950s. If we had done so, the number of lung cancer cases would have been considerably reduced. Unfortunately, we were not really sure of either causation or dose-response kinetics. Add to that the important financial considerations, the all-too-familiar ability of one generation to forget the lessons of an earlier one, and the jurisdictional problems already made clear in the capsule history above, and we can understand (but not condone) the delays in getting protective measures going.^(b) By the time the validity of the U.S. scientific results was established, the biological damage had been done. Let us hope our current problems with chemical pollutants in the environment do not have to go down this dreary path of repeating the past no matter what lessons it can teach.

Space prohibits recounting the numerous steps taken once the danger was fully appreciated. These can be seen in the JCAE hearings, FRC reports, numerous notices in the *Federal Register* (1967, 1968, 1970, 1971), and reports from the IUMRRG (final report in the 1971 *Federal Register* cited). For our purposes, it is worth noting how completely the situation changed from failure to act on recommendations from fully credible sources to an avalanche of demands for action and better (i.e., lower) standards. Agencies and individuals vied with each other for the position of savior (e.g., the Secretary of Labor and the Secretary of Health, Education and Welfare). Fortunately, the work of the PHS has been adequately, although not fully, recognized. It was, however, the FRC's work that, in this writer's opinion, really brought about the reversal of attitude. This does not seem to be generally appreciated. The coalescence of federal agencies in the council was the catalyst that got the reaction going^(c) in the early and middle 1960s.

C. Other Uranium Mines

The postwar study of the Czechoslovakian uranium miners was reviewed first by Horáček, (1969) and assembled in detail by Ševc, Kunz, and Plaček (1976); Kunz, Ševc, and Plaček, (1978); and Kunz et al. (1979) among others. There are problems in identifying how many miners were in the two major groups, those who

- (a) Remember how foolish the idea of fungi in the mines seemed as a contributing factor? Professor Dr. V. Wolf at Karlsruhe recently drew this author's attention to a paper by a microbiologist of the Laboratory ORL of the Czechoslovak Academy of Sciences (Kusák 1969) that describes the large number of fungal conidia inhaled by the miners and the balance of antimycotic and mycotic effects. Of special interest is the production under certain conditions of the potent biological carcinogen "Aflatoxin" by *Aspergillus flavus*, a frequent component of the fungal population. No proof exists that it takes part, but it could some of the time.
- (b) The atmosphere of the times played its part too. In the early 1950s, the United States was busy establishing a nuclear industry, both military and civilian. The public was fairly solidly behind the effort. People who advocated shutting down uranium mines because of not-yet-proven health hazards were likely to be viewed as subversive.
- (c) Several histories of radiation protection activities are now in preparation. It is assumed that further details on these matters, which are beyond the purview of this book, will appear in one or more of these.

started mining between January 1948 and December 1952, and those who started between January 1953 and December 1957. It appears that there are about twenty-five hundred persons in the first group and nineteen hundred in the second (NCRP 1984a). Excess lung cancers in the first group are 169 through 1973 (i.e., 212 observed versus 43 expected). The second group was exposed too recently to be used currently. The exposure categories range from 72 to 716 WLM. There were over 120,000 radon measurements made.

Risks calculated for this group are higher than those in the U.S. group by a factor of two to three. On the whole, the Czech study appears useful and comparable in reliability to the U.S. work (Evans et al. 1981). The difference in calculated risk may or may not be significant. No explanation is apparent.

The Canadian uranium miners contributed the third postwar group for epidemiologic study. Uranium mining began in Canada in 1954, with a peak of eleven thousand miners employed. However, duration of employment and exposure declined by 1965, and radon daughter measurements were not as numerous in the early years of maximal employment as in the later years of reduced employment. The record-keeping has been exemplary through what is known as the Ontario Uranium Nominal Roll. It contains over fifteen thousand names; eighty-one deaths have been certified as due to lung cancer, about twice the number expected. Risk estimates for this group are about the same as for U.S. miners. However, the study is really too young to have the same quantitative significance as the U.S. and Czech work. In the future, it will be more mature, but the exposures have declined considerably, and they were never as high as in the other studies (only 21 to 180 WLM in three categories).^(a,b)

D. Other Miners

Miners working in a variety of hard-rock mines are expected to exceed normal incidences of lung cancer because these mines frequently have concentrations of radon daughters well above background. The levels are seldom as high as in uranium mines, but they are significant nevertheless. Formal studies, as related earlier, have been carried out for Swedish iron, zinc, and lead miners; fluorspar miners in Newfoundland; British underground iron miners; U.S. base-metal miners working underground in hard-rock formations; and South African gold miners. Some of these were described in the 1972 UNSCEAR report and expanded upon in the 1977 version (UNSCEAR 1977). The Newfoundland and Swedish populations are also reviewed in some detail in the most recent BEIR report (BEIR III 1980) and the very recent NCRP report (NCRP 1984a).

The total population in Newfoundland's mines is 2,414, with records over the period 1933 to 1971. Estimated radon daughter concentrations were 2 to 8 WL up to 1960, below 0.5 WL since 1960. There was a clear increase in incidence of lung cancer, which correlated well with cumulative exposure. The complications of smoking are analyzed. Risk estimates per unit radon daughter exposure are in the same range as those derived from the uranium miners. (The cogent references can be found in BEIR III.)

The Swedish metal miners, composing a small group, have the advantage of very long follow-up times. BEIR III concludes that the data are insufficient for determination of risk coefficients. However, others have calculated tentative risks in the

(a) A recent addition is miners being traced through the Workman's Compensation Board.

(b) Further details can be found in the paper by Stewart et al. (e.g., Myers and Stewart 1979).

Swedish miner group. Two of the three groups appear to have considerably higher risk than the uranium miners. If true, it may indicate greater importance of factors other than radiation exposure. However, the study is still in progress, and the Swedish investigators need more time.

The British hematite miners showed a significant, but not large, excess of lung cancers. Exposure levels were low (0.15 to 3.2 WL). Even lower exposure levels (0.1 to 0.2 WL) were reported for the U.S. base-metal miners. These populations contribute little to the total picture because of the low exposure levels. The South African gold miners, who show no excess of lung cancer, had comparable exposure levels (0.1 to 0.3 WL on the average).

E. Commentary on the Epidemiologic Results

Even the brief summary given above indicates that research on the epidemiology of radon daughter effects has been active in many parts of the world. Relative to many of the research undertakings concerning radioactivity and health, the U.S. contributions have been significant, but do not preempt the field as they have in some other areas. Yet, the contributions of U.S. work, including the later years of the AEC, are significant and of as high quality as can be mustered in a field with so many difficulties.

The primary reasons for engaging in and supporting these activities are (1) the contribution they make toward establishing dose-response relationships, (2) the development of estimates of risk, and (3) the establishment of standards.

We saw in chapter 1 that the radium data, among the best we have, can support more than one interpretation of dose-response relationships, particularly in the low-dose domain. The data from the uranium miner studies contain less congruent populations and a less certain estimate of dose. The easy way out is to assume linearity as conservative and decide that the data are "not inconsistent" with a linear expression. This may be as far as we will ever get, but continuation of the work until every possible data point has been gathered is important.

Risk estimates from the miner data cover a surprisingly narrow range when the wide separation of sources and populations is taken into account. UNSCEAR (1977) remarks on the higher cancer induction rates derived from mortality experience in uranium and other miners compared to radiation from external sources (i.e., 10 to 25 $\times 10^{-6}$ /rad or kerma of absorbed dose in the Japanese bomb survivors and British spondylitics versus 40 to 180 $\times 10^{-6}$ /rad or kerma for the miner populations).^(a) If true, this may indicate that a cofactor or cofactors in the mine exposures is influencing the incidence rates. However, in view of the problems of establishing the radiation dose in the Japanese populations and the many possibilities for error in the miner studies, these estimates do not seem alarmingly different. Indeed, despite the much-discussed problems of the miner epidemiology, the final figures seem to have reasonable consistency and indicate that the whole effort is worthwhile. A composite graph showing effects in all of the human epidemiologic studies it is feasible to plot, as well as summary data from the animal experiments, is shown as figure 3.2.

(a) BEIR III gives revised figures of 22 to 45/10⁶/yr/rad for the miners versus about 3 cases/10⁶/yr/rem for the Japanese bomb survivors and the British spondylitics.

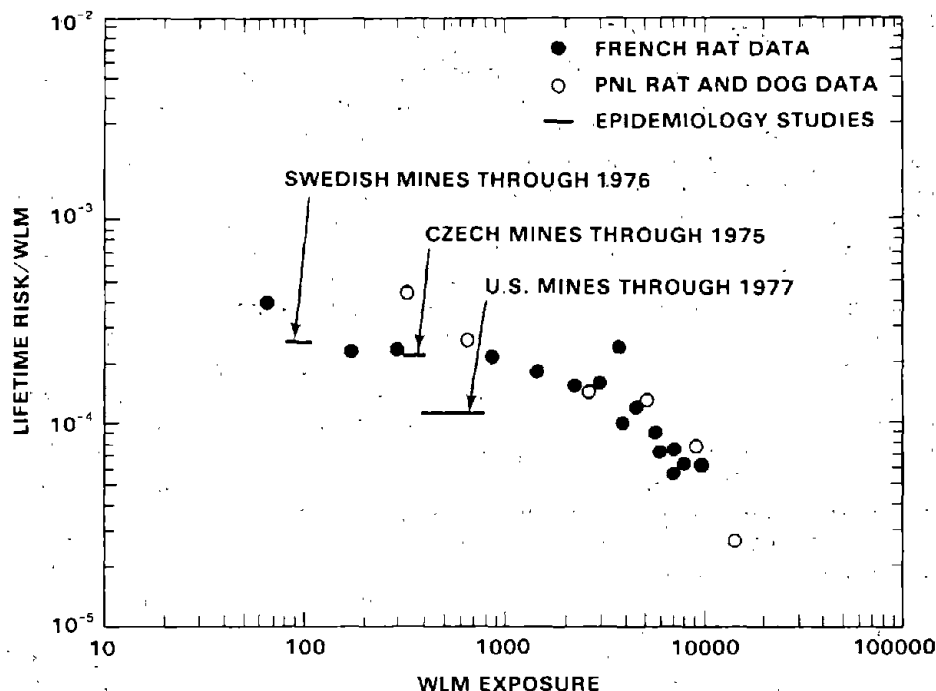


FIGURE 3.2. Composite of dose-effect relationships on the basis of cumulative exposure. (Courtesy of F. T. Cross, modified from figure 11.1 in NCRP 1984a.)

Also of use to the reader is the very complete summary of published dose calculations and derived occupational exposure limits from the many studies contained in this chapter given in table 4.1 in NCRP Report 78 (NCRP 1984a).

The establishment of standards for the miners is a book in itself. Every major report of epidemiologic work has either been issued with implications for allowable exposures or has had figures derived by others for this purpose. We are greatly indebted to Fredrick Cross and coworkers at Pacific Northwest Laboratory (PNL) for the sophisticated in-depth evaluation of methods for setting occupational health standards for uranium miners already mentioned (Cross et al. 1974). This report considers all aspects, but especially useful for our needs is its table 2.3, a summary of published dose calculations, epidemiologic findings, and recommendations for exposure standards from the original Evans and Goodman paper (1940) to the work of Harley and Pasternack in 1972. This table resulted from a project development report prepared in 1968 by an ad hoc task force from PNL (Cross et al. 1968). It provides not only succinct analyses of the scientific problems, but full details of all research and development programs in progress, including their sponsors and coordination of other Battelle programs with them. Suggestions for research abound. These include the conclusion that much more needs to be done on the uncombined radon daughters and their role in producing biological effects.

An updated version of all of this work is reproduced in the recent NCRP report (NCRP 1984a).

VII. The Spas and Therapeutic Mines

It should be no surprise that radon found favor as a therapeutic nostrum much as did ^{226}Ra (see chapter 1).^(a) There are many areas of the world where high concentrations of radon and its daughters exist in natural water supplies. In addition, many former mines with high radon concentrations in the air have been pressed into service as treatment centers, and special chambers called "emanatoriums" have been constructed at major medical centers. The uses of radon water go back to antiquity, while the use of air with high radon concentrations developed primarily in the early twentieth century.

The purposes were identical to those of the therapeutic injections of radium: "stimulation" of bodily functions to combat various chronic diseases or the nonspecific ailments of advancing years. In contrast to the uses of radium, which occurred to a large extent in the United States, these practices were much more centered in Europe. The famous hot springs (i.e., spas) of central Europe were paramount centers. Many of them were located in areas with the same geological formations as at Schneeberg and Joachimsthal. They had waters with both high temperatures and high contents of dissolved radon.^(b)

The total populations exposed may have been of the same order as those given radium as a nostrum. We have no adequate records, at least none that have been analyzed. Fortunately, the short half-life and short retention time of radon and most of its daughters meant short exposure times for all exposed persons, save the workers in these establishments. There has been no epidemic of radiation-induced lesions to put beside the uranium miner saga or the radium saga. Nevertheless, some interesting work has been done that deserves review. In a sense, it is more observational than experimental, and the U.S. participation has been relatively minor. Yet, it is a part of the history of radioactivity and health.

A. The Spas and Therapeutic Galleries in Europe

Typical of the great European spas is Badgastein, in the Austrian Alps. In an enthusiastic book written by Hans Hannau, a Floridian, we read the following:

For Badgastein sits within a framework of Nature's most magnificent scenery. It is an international resort and health center . . . an interesting town in which to meet celebrities, kings, maharajas, beautiful women, statesmen, actors, poets and composers from all over the world. (Hannau, undated, inside front dust jacket)

There are eighteen or more radon-containing springs at Badgastein, whose water is transmitted by a system of pipes and tanks to the central watering areas and even to the individual hotel rooms. The water is either drunk or bathed in, according to the prescription of the attending physician.

In addition, Badgastein and other centers now have what are known as thermal galleries. For example, a worked-out gold mine was found to have high concentrations of radon and also, perhaps because of the proximity to the hot

(a) This is separate from the use of encapsulated radon sources in therapeutic radiology, where it is the gamma radiation that is important.

(b) The "metered radon solutions" of Russia and Eastern Europe (see footnote b, page 165) were prepared in laboratories and distributed to the points of therapy. Details concerning these have been described by Andreev (1984) in reference material kindly supplied by Dr. Carl Reich (see next section).

water sources, quite high ambient temperatures. Again we will let Hannau give the details:

...an unexpected increase in temperature was remarked within the recesses of the mine. Chemical research disclosed that this was due to secondary uranium deposits contained in the rocks and compassing a thin layer over the walls of the tunnel. [This was, of course, *not* the source of the high temperatures.] The deposits were rich in radon. Workers at the mine who suffered from rheumatism soon found themselves feeling better. And here for the first time was apparent evidence that radon emanations were effective as a curative treatment for certain ailments.

These Stollen, or tunnels, are almost a mile and a half long. The temperature within rises to almost 90°F. Visitors proceed through the *Stollenkurhaus*—the Air Spa Building—immediately adjacent to the Galleries, whence they proceed on trains through the tunnels, with special nurses in attendance. The natural hot-air emanations are used in the treatment of illnesses that are favorably affected by a combination of warmth and inhalation of radon. Chronic inflammatory forms of rheumatism, inflammations of muscles and nerves, disturbances of the vertebral column, gout, certain circulation disorders, sequels to poliomyelitis, certain allergies, and hormonal and vegetative troubles are treated here. The results are considered as favorable as those of the thermal baths and, in many cases, more so. (Hannau, undated, p. 49)

Figure 3.3 gives an idea of the extent of development around one of these thermal galleries, while figure 3.4 illustrates the opulence of a resort like Badgastein.

A summary of the medical benefits alleged to be associated with treatments at these resorts is the following:

The effects of the waters, according to some medical writers, are based on at least three factors: the general stimulation that every watering cure produces; the special properties peculiar to natural hot water; and, finally, the effects of the inert gas radon contained in the thermal waters. The last is not to be confused with the effects of radioactive matter in concentrated form which is stored in the body. This gaseous radon is exhaled or eliminated from the body after a very short time (normally two to four hours), whether absorbed by inhalation, drinking, or bathing. In the process, however, the radon stimulates the functions of all the body cells, relieves pain, in neuritis and rheumatic complaints, and provides a special stimulus to the endocrine glands. . . . The source of the foregoing statements is the writings of various medical authors. (Hannau, undated, pp. 16, 47)

This language is typical of that used since antiquity to describe these "cures." As scientists, we tend to dismiss them as mostly psychosomatic or figments of the imagination. Yet, the field of toxicology is rife with instances where low doses of otherwise harmful substances appear to "stimulate." In the radiation field, we have now a formal collection of such instances, with the research behind them in a book by Luckey (1980), and more recently, a symposium, the proceedings of which are yet to be published. Only the future can tell.

Figure 3.5 illustrates one possible reason that at least the male customers feel "stimulated" and in improved health after such a treatment. Parenthetically, one must wonder at the radiation exposure of such attendants if they should work for long periods in these thermal galleries.

B. Spas and Therapeutic Mines in the United States

While the United States has a good supply of hot springs, few if any have been used for radon treatments in the manner of the European spas. What interest



FIGURE 3.3. Main building and entrance to thermal rock galleries at Boeckstein. (Hannau undated. Reprinted with permission of the author.)

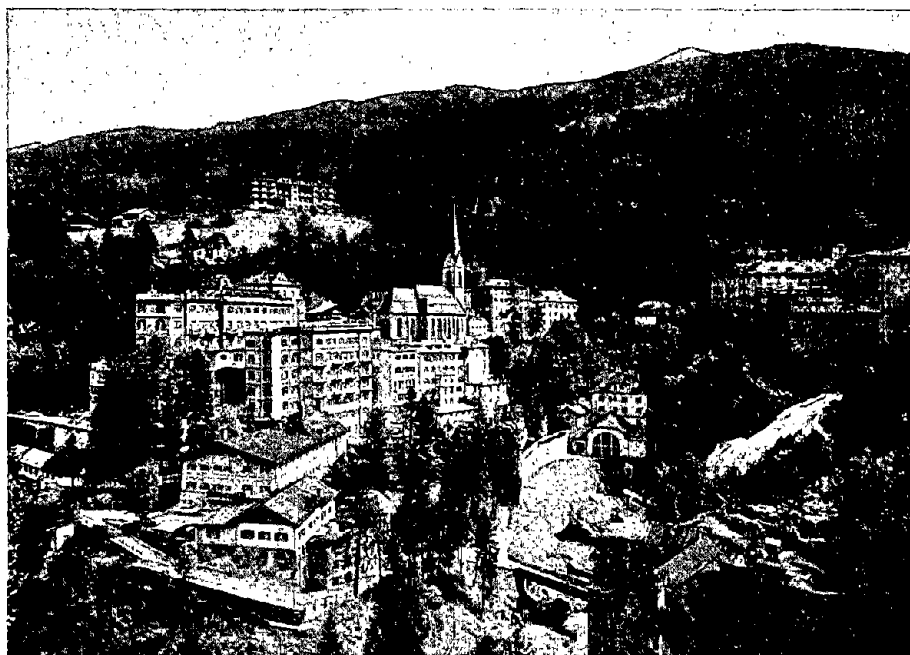


FIGURE 3.4. General view of Badgastein. (Hannau undated. Reprinted with permission of the author.)



FIGURE 3.5. Treatments in the thermal gallery, Badgastein. (Hannau undated. Reprinted with permission of the author.)

there is has been of relatively recent origin. A worked-out uranium mine in Montana has received the most attention. In a small book entitled *Arthritis and Radioactivity*, Wade V. Lewis tells the story of Montana's Free Enterprise Uranium-Radon Mine. It is hardly as opulent as Badgastein, but testimonials are as numerous and enthusiastic. This mine is not at high temperature, and the principal exposure is thus to radon and its daughters (Lewis 1955).

When a topical symposium of the Health Physics Society was held at the venerable spa at Saratoga Springs, New York, the levels of radon and of radium in the waters were considered informally. However, nothing about this appeared in the published proceedings. There was a paper given by people from the Environmental Protection Agency on ^{222}Rn in potable water (Gesell, Pritchard, and Hess 1982). They reported on radon content of water for seven areas of the United States, and in Finland, Great Britain, Japan, New Zealand, and Israel. No special effort was made to concentrate on spas.

C. The Radon Levels Involved

A considerable effort was expended by Austrian, Danish, German, and Czech investigators to determine the concentrations of radon in the thermal galleries. These considered primarily the amounts in the water and in air, but secondarily amounts in blood, excreta, etc., and "metabolism" of the several nuclides.

Amounts in air clustered around 10^{-9} Ci/l, i.e., in the same range as the air in the mines.^(a) Recalculated in working levels, the amounts in air range from less than one to as high as about 100 WL. The amounts in water around the spas tended to be higher in general, with average maxima from 1,000 pCi/l to 10,000 pCi/l. Measurements around Badgastein can be found in Pohl-Rüling and Scheminzky (1954), Aurand, Jacobi, and Schraub (1956), Aurand et al. (1960), and Pohl (1962). Concentrations in natural waters around other European spas are given by Hursh et al. (1965).^(b) This last report includes an average maximum of 2,000 pCi Ra/l in water at a spa named Kronthal (Taunus). Some of this research considers also radon concentration in free air in the neighborhood of the spas. Pohl-Rüling and Fischer (1982) quote a mean concentration in the water at Badgastein of ^{222}Rn at 4,000 pCi/l, while the atmosphere in the thermal gallery had a mean concentration of 3,000 pCi/l. Also, Gesell, Pritchard, and Hess (1982) present the range for a large variety of samples, e.g., 0 to 30,000 pCi/l with 25% of the locations exceeding 2,000 pCi/l and 5% exceeding 10,000 pCi/l. Andrews and Wood (1974) report ^{226}Ra , ^{222}Rn , and ^{210}Pb levels in the waters of Bath, England, and show levels of ^{222}Rn well over 2,000 pCi/l.

Measurements are not readily available for the therapeutic mines in the United States. The more legitimate ones^(c) are near ore bodies of the same or lower uranium content as the European therapeutic galleries. Levels of 1,000 pCi/l or below would therefore be expected.

Of special interest is early work from Copenhagen by Jansen and Schultzer (1926). Jansen was "Director of the Emanatorium" at the Radium Station of the Finsen Institute of Copenhagen and was searching for the "optimal therapeutic

(a) Some of the earlier reports were in "impulses/min," and these have been converted very approximately.

(b) We will consider springs not associated with spas in section X.

(c) There are some that consist only of caves lined with uranium placed there by the owners. These contain little radon.

level" of radon to use in his emanatorium. They state that their original doses were very small, e.g., 1,000 M.U. (Mache units) daily by mouth, or 2 to 4 M.U./l of air in the emanatoria. These convert to about 700 to 1,400 pCi/l or 7 to 14 WL in the air assuming equilibrium with radon daughters; no reason for any great worry for short exposures. However, they quote also increasing the dose to as much as 300,000 M.U. (about 10^{-4} Ci/l) in the water and 5 to 600 M.U./l (1,800 to 218,000 pCi/l or 18 to 2,180 WL) in the air, assuming equilibrium. Even at these levels they reported not much obvious effect either therapeutic or deleterious. Indeed, the authors worried more about the gamma dose from the degradation products deposited on the walls and floor of the emanatorium than the internal dose from radon and its daughters.

D. The Possibility of Effects

We have already remarked upon the multiplicity of testimonials and the enthusiasm of patients and physicians for the alleged therapeutic effects of these exposures. Organized scientific medicine still regards these as in the realm of folklore, and we can go no further at present, except to say that perhaps nature has not yet revealed all of her secrets to us.

Fortunately, as mentioned earlier, the short physical half-life of radon and its early daughters plus rapid elimination from the body (biological half-life less than one hour, Suomela and Kahlos 1972; Hursh et al. 1965)^(a) have spared us a repetition of the deleterious effects seen in the iatrogenic cases of poisoning by ^{226}Ra , ^{228}Ra , and ^{224}Ra . Admittedly the single doses have sometimes been high, but they are short-lived. Long-term epidemiologic study of the thousands of patients who have "taken the cure" over the years would probably be fruitless. On the other hand, long-term effects on hematopoietic tissue or production of lung cancer might conceivably occur in the employees who conducted patients into the galleries and ministered to their needs during the therapy sessions. The numbers of such employees may be too small to support bona fide epidemiology. Nevertheless, follow-up of these individuals should not be dismissed out-of-hand. For example, Pohl-Rüling and Fischer (1982) have studied chromosome aberrations in inhabitants and workers at Badgastein. There were definite increases in aberrations in persons continually irradiated by the environment, and a dose-response curve could be drawn. However, no link could be established between the presence of these changes (mostly dicentrics) and deleterious effects, i.e., pathology.

At the 1973 Congress of the International Radiation Protection Association, several Japanese investigators (Maeda et al. 1974) attempted to distinguish between the cause of death in a population living near a "radiation-rich hot spring" and a regional cohort. No noticeable difference was found.^(b)

(a) Hursh et al. measured loss by direct measurement in volunteer subjects who drank radon water using breath, blood, and urine for radon and a whole-body counter for RaC, while Suomela and Kahlos used the ^{214}Bi elimination only.

(b) Very recently, Carl J. Reich, M.D., provided this author with a draft note intended for the journal, *Health Physics*. He states that over 100,000 individuals have visited the radon mines near Boulder, Montana, and he refers to a clinical study of a portion of this population. He also states that up to one million patients are treated annually in the spas of "radon laboratories" of Russia. Perhaps there is, after all, a population large enough for epidemiologic study. Dr. Reich also gives a few estimates of dose in units of working level (Reich 1986).

As will be seen from the titles of the several papers quoted in this section, a reasonable amount of pharmacodynamics was done over the years around these exposure modalities, some of it of considerable value to the uranium miner problem since relatively little experimental work has been done with the miners.

This is an area of more interest than substance from the standpoint of research. However, as a facet in the history of radioactivity and health it presents items of interest and some unanswered questions. It has recently been expanded greatly in the area of possible indoor exposures in a variety of situations. A later section will consider these very recent additions.

VIII. Experimental Animal Research

A. Early Studies

We have already alluded to some of the earlier experimental work on radon with animals. It almost always utilized quite high concentrations, and there was little understanding, of course, of the role of the daughter products. This makes attempts to reconstruct the doses very difficult. About all these early experiments did was to show that radon was a toxic gas.

The animal experiments up to date of writing have been summarized well by Morken (1955c), by Cross et al. (1968, 1974, 1986), and in NCRP (1984a). The chronology begins in 1904 with some Russian work by London (1904); a dissertation by Gol'dberg (1904); and some French work by Bouchard, Curie, and Balthazard (1904), and Bouchard and Balthazard (1906). These were all very acute exposures.

Work in the Emanatorium (Copenhagen) by Jansen and Schultzer in 1926 showed that suckling rats were more sensitive than adults. It was followed by a rather ingenious second experiment (Schultzer 1926) to separate effects of the radiation within the animals from the "hard" radiation outside the animal arising from the decomposition products deposited in the Emanatorium. They placed a radium source in a paraffin capsule inside the animal. The radon could diffuse through and enter the blood stream, thus irradiating the animal internally; but the radium did not dissolve. They kept the cage well ventilated with room or outside air so that no radon or daughters would enter by inhalation. Strengths of the radium-bromide solution in the capsule were adjusted to provide internal radon concentrations similar to those after inhalation in their first experiment. These "capsule" animals were observed for nine weeks, and no biological effects were seen compared to the controls. Therefore, the authors reasoned, the effects in the first experiment must have been from the hard radiation (i.e., gamma rays) which bombarded the animals from without. Alas! So near and yet so far! They recognized the role of the daughters formed outside of the animals, but muffed the concept of their importance on inhalation.

The acute and semiacute experiments that utilized the inhalation route demonstrated marked effects in the lungs and other tissues such as hyperemia, generalized inflammation, etc., but no lung cancers. In the tradition of all animal toxicology, until the postwar work showed the way, the investigators were too impatient and nearly always terminated the experiments during the latent period for the development of cancer. This early research, including German, Austrian, and Czech work cited in the reviews, also established many facts about the metabolism of radon. However, even as late as World War II

(e.g., Lorenz 1944; Hollcroft and Lorenz 1951) the animal work did not really imitate the miner exposure situation. Also, only the work of Read and Mottram (1939) and of Jackson (1940) addressed the maximum permissible (tolerance) exposure levels directly.

B. The Post-World-War-II Years

Even though the AEC was slow to support epidemiologic work with the miners or control work in the mines, it quickly encouraged and supported animal studies with radon. Centers for such work were the Rochester Project and later Pacific Northwest Laboratory and Colorado State University. At the same time, the Commissariat à l'Energie Atomique (CEA) in France mounted a rather extensive experimental program with animals. Some work was done at other laboratories such as the Naval Radiological Defense Laboratory (Cohn, Skow, and Gong 1953), but these studies did not continue for extended periods. Projects at Rochester, CEA, and PNL have continued over two to three decades.

A full review of much of this work can be found in the proceedings of the many meetings and organizations we have already discussed. We will review what was done primarily for highlights and from the standpoint of concepts and philosophy and leave the details for these reviews.

1. Work at the University of Rochester Atomic Energy Project

Animal research on radon at Rochester began with the checks by Shapiro and Bale on Bale's ideas regarding the role of the inhaled daughters. This was described in the dosimetry section.

Work aimed at measuring effects began with the Ph.D. thesis of Donald Morken in the mid-1950s. The first experiment used mice and an exposure rig (Morken 1955b) that essentially removed all of the preformed daughter products from the circulating air. He determined the LD_{50} for thirty days. When calculated in terms of absorbed energy in ergs per gram, the LD_{50} was very similar to that of 250-kV x rays.^(a) In view of the vaunted extra biological effectiveness of alpha particles, this result was a surprise, but there was no doubt about it (Morken 1955a,c). Also, the tissue pathology looked very similar to effects from acute x-irradiation (Scott 1955). It could only be concluded that, for the processes causing acute deaths in these mice, there was little dependence on the type of radiation employed.

There were some differences in the pathology between radon and x rays when a less acute dose was given. This work permitted observations up to seven months (Scott 1955). Proliferation of bronchial epithelial cells was obvious, and there were kidney changes reminiscent of those seen after intravenous injection of ^{210}Po (see chapter 4).

(a) Morken expressed his doses as an activity-time product, mCi-hr/l. This was before the working level had come into general use. Also, since the exposures were to almost pure radon, the working level notation could not apply anyway. Locally this unit of Morken's was referred to as "The Mork" somewhat in analogy to the old Mache unit. However, this usage never got into print or beyond "in-house" discussions. It is unfortunate in many ways that some such unit for radon exposure has not found general use. We are now in the situation where radon gas is recorded as a concentration only (e.g., picocuries per liter) while the unit for the daughters includes a time factor, i.e., working level month. The alternative is to put the daughter unit back to a concentration only.

Later reports used large enough groups of animals to measure life-span shortening, body weight, and the hemogram (Morken 1961, 1964; Morken and Scott 1966). Life shortening was proportional to total accumulated dose. On a multiple-exposure regime, it appeared that the lethal injury was half repaired in two weeks.

Of particular interest in these experiments, and still unexplained, is the fact that the red cell count remained depressed for a considerable period or even permanently. It did not recover nearly as rapidly as after treatment with external radiation sources. On a multiple-dose regime, the red cell count was depressed by a fixed amount following the first dose and remained at this level for about one year. It then merged with that of the controls. It was not further influenced by additional doses. Following a single larger dose, it just remained depressed for a year or more.

Radon produced less life shortening in the mouse, per unit of radiologic dose, than did injected ^{210}Po .

In none of these experiments were any true lung cancers found, even though there were some indications of metaplasia. It began to look as though even modern animal experiments were going to have difficulty reproducing the lesions seen in the miners.

At about this time, the Rochester group turned to a larger, more elaborate exposure system, which could accommodate many small animals and a few dogs simultaneously. It contained steady-state concentrations of the daughters at fractions of the equilibrium value on the order of 0.9, 0.45, and 0.25 for RaA, RaB, and RaC, respectively, and about 20% unattached RaA activity (Mercer and Stowe 1970). In toto, these experiments involved about two thousand mice, one hundred rats, and eighty dogs, plus suitable controls. Details of the results can be seen in the Morken references given below and in NCRP Report No. 78 (1984a).

The work with mice was chronic, with cumulative exposures up to 72,000 WLM and average total doses to lung up to 11,000 rad. There were several experiments with different exposure periods (Morken 1973a,b). There were some serial sacrifices and emphasis on gross and microscopic pathology rather than life-span shortening.

Again, precancerous changes were seen regularly. There were tumors much like those that arise spontaneously, but they showed a greater tendency toward malignancy. On the whole, however, the pathological changes were still not very similar to the bronchogenic carcinomas seen in man.

The exposure of the dogs was also chronic. Calculated working level months in dosimetry and pilot experiments were 1,950 or 3,900 and a tracheal dose of about 10,000 to 20,000 rad. There was also a large exposure-response study with fifty-one dogs and exposures from 200 to 10,000 WLM. The pathological changes were classed as "subtle" and largely inflammatory, and they were not clearly related to dose. No frank cancers were found. Even a special experiment giving tracheo-bronchial doses up to 50,000 rad did not change the picture (Morken 1973b).

The work with rats involved average doses to lung of 4,300 rad and much higher doses to the trachea. Again the pathological changes were not impressive, although some metaplasia appeared in lungs.

The Rochester experiments during the period of pertinence to this book were thus notable for the lack of production of radiation-specific tumors. The only permanent changes in the lung were in the alveoli, and they were not of the type expected to lead to cancer.

2. Work at Pacific Northwest Laboratory

The experimental work with animals at PNL began later than that at Rochester. It differed in having the Syrian Golden hamster replace the mouse, and in emphasizing exposures to aerosols of radon and daughters mixed with other possible causative agents in the mines, such as uranium ore dust and diesel exhaust fumes. Also, dogs were trained to smoke cigarettes,^(a) and thus an overt study could be made of the possible effects of tobacco smoke with and without exposure to the surrogate mine aerosols.

The exposure chamber array was quite elaborate. For the hamsters, it consisted of a special plexiglass chamber into which cages could be placed. For the dogs, the exposure was of the mouth and nose and nose-only type. The cigarette smoking was arranged through a special mask that was not used simultaneously with the experimental aerosol exposures. The chamber arrangements are shown in figure 3.6.

The work with the Syrian Golden hamster involved over six hundred animals in six groups with various combinations of radon and daughters, with or without uranium ore dust, uranium ore dust alone, diesel engine exhaust alone, and one group with everything plus the usual controls. The uranium ore dust was carnotite.

Several neoplastic lesions were seen in the group receiving radon and daughters and in the group receiving also uranium ore dust. Lung tumors appeared in these same groups at exposures above 8,000 WLM. There was severe squamous metaplasia in the group that received everything. The tumors were, on the whole, not particularly invasive, with one exception.

Other respiratory-tract lesions were quite general. The uranium ore dust and diesel fumes alone provoked inflammatory and proliferative processes, but no precancerous lesions.

The incidence of true cancer was still relatively low. Only four hamsters from over five hundred experimental animals developed squamous carcinoma. This was a greater incidence than in the Rochester experiments, but it was hardly a large increase. It led the investigators to conclude that the Syrian Golden hamster is refractory to carcinoma induction, especially to agents of low carcinogenic potential, and that it is not a good animal model for respiratory cancer in man.^(b)

The experiments with beagles involved sixty-nine animals, including nine controls that received room air. The others were equally divided into groups receiving radon and daughters and uranium ore dust, the same plus cigarette smoke, and cigarette smoke alone. (Support for this work came primarily from AEC until the later phases, which were supported also by the NIEHS.) There was no work with diesel exhaust fumes in the dog experiment.^(c)

There were eight lung neoplasms in the nineteen dogs remaining (dogs had been removed earlier for detection of early effects) that had received radon plus daughters and uranium ore, two in the group receiving the same but also smoking cigarettes. The dogs that smoked but did not receive radon, or radon

(a) The beagles became quite fond of their daily smokes, or so it seemed.

(b) The reasons for choosing this species in the first place will be taken up in chapter 9.

(c) An extensive study of the toxicology of diesel exhaust aerosols is under way at the Inhalation Toxicology Research Institute, Lovelace Foundation (ITRI 1979) as part of the "new look" for former AEC-ERDA Laboratories.

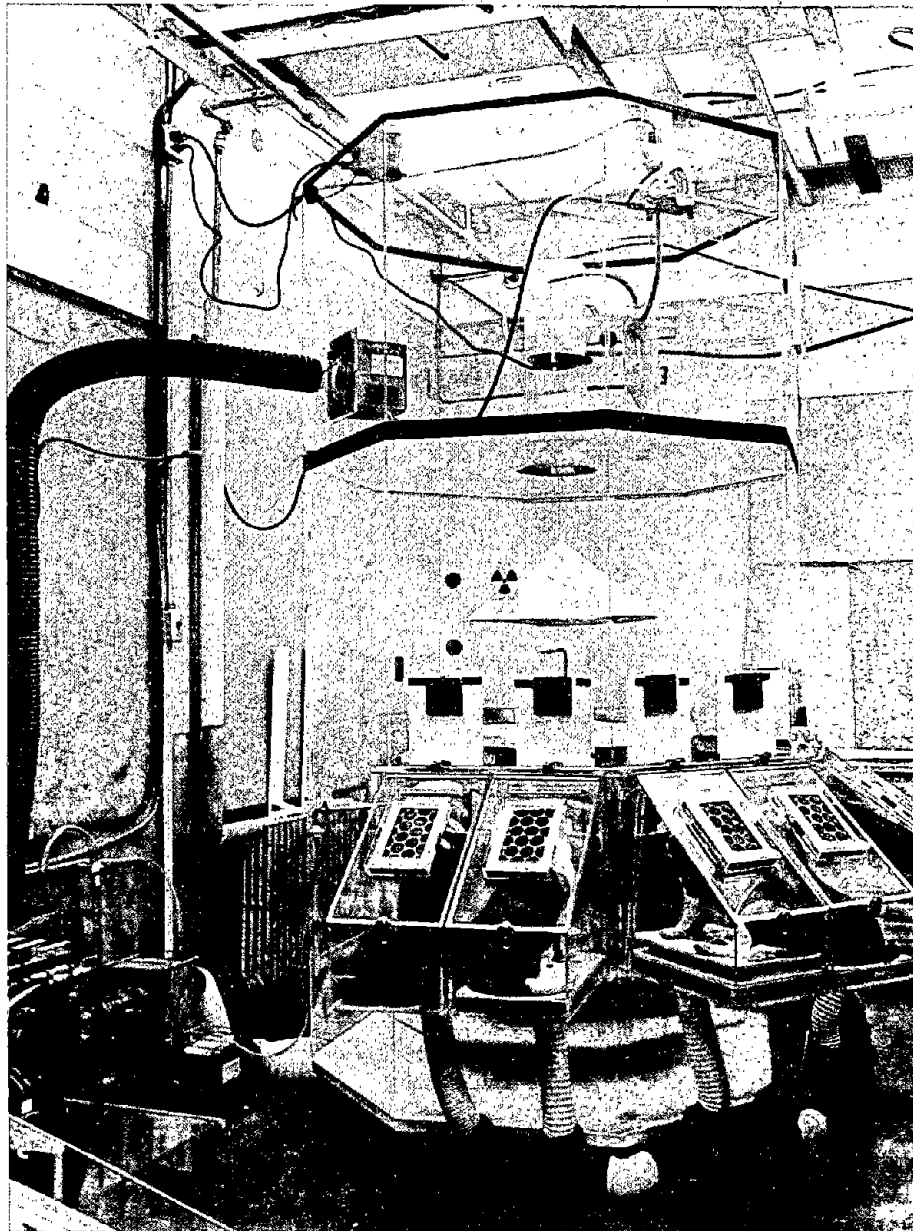


FIGURE 3.6. Exposure chamber designed for head-only exposures of ten dogs to radon daughters with uranium ore dust as used at Pacific Northwest Laboratory. (Reprinted from Cross et al. 1978, p. 56.)

in combination with other substances, showed many pulmonary changes, but not lung cancer. As in the hamsters, the animals developing tumors had quite high cumulative radiation exposures. In general, the development of lung cancer in both of these experiments at PNL occurred only at doses nearly two

orders of magnitude higher than those associated with lung cancer in the miners.^(a) The authors speculate that one reason may lie in the shorter life span of the animals compared to man. The longer human life span may allow more time for carcinogenesis to be expressed. Also, the dose nominally calculated in the animal work may be overstated because of "wasted radiation" (i.e., a lower dose may have initiated the process, but the life span was over before it could be expressed).

The fact that cigarette smoke seemed to mitigate rather than increase the effects of radon was again something of a surprise. The authors suggest increased thickness of the mucus layer and a net stimulation of mucociliary clearance as possible reasons. We have already encountered this idea in the human studies. When respiratory-tract tumors developed in animals, they originated in the bronchi, alveoli, or nasal septa. The tumors in the uranium miners are bronchogenic and primarily in the smaller bronchi. This difference may represent a species difference or dosimetric difference because of the smaller dimensions of the animal's pulmonary tree, an issue that cannot be decided at the present juncture.

There were many follow-up studies, including exposures of dogs to carnotite uranium ore dust alone, i.e., without radon or daughters, and a fairly extensive program using rats exposed to mixtures of radon plus daughters and carnotite ore dust. These were intended to develop dose-response curves, and the exposures were not life-span.

The results^(b) in the dogs suggested differences in the pulmonary lesions when exposure was to ore dust alone and slower development and reduced degree of pulmonary fibrosis when radon plus daughters were absent. The rats showed no change in mortality patterns at exposures up to 2,500 WLM, but there was significant life-span shortening at 5,000 WLM (about 1,000 rad mean lung dose) or more. Interesting phenomena appeared in the occurrence of lung carcinomas in the rats. There was an increase in apparent lung cancer risk with decrease in radon daughter exposure rate (life-span effect?), with an increase in the portion of *unattached* radon daughters, and an increase in radon daughter disequilibrium. It also appeared that the ore dust contributed to the prevalence of nonneoplastic lesions, but not to the development of tumors, at least at the higher radon daughter exposure levels studied. Thus, this new research confirmed what was clear from the earlier work, i.e., that it is possible to produce frank lung tumors in animals with radon plus daughters alone. It also indicated that there are still unresolved questions. In addition to those involving unattached atoms, disequilibrium, and exposure rate, the chances of some species differences persist. These will be seen again in the French work about to be discussed.

3. Animal Studies at the Commissariat à l'Énergie Atomique, Razès (Limoges), France

The French not only have a strong nuclear energy program but have engaged in much supporting research. Lafuma's laboratory has been active in

(a) Lung cancers were subsequently observed quite late after exposure in a few animals (not in the life-span experiment) exposed to much lower levels of radon daughters (Cross, private communication 1984).

(b) The author is indebted to F. T. Cross for a specially prepared summary of these relatively recent and ongoing experiments at PNL.

internal-emitter research for many years. The radon work is moderately recent and was another overt attempt to correlate animal carcinogenesis with events in the uranium mines. The test animal was the rat (Sprague-Dawley).

The French investigators used moderately large chambers for their early work. These could hold up to one hundred animals and contained an atmosphere in which decay products were reduced to about 0.01 of equilibrium. Later they used a very large chamber holding about three hundred rats and an atmosphere of radon either in full equilibrium with daughters, 20% to 30%, or as low as 1% of equilibrium. In some experiments, either stable cerium hydroxide or uranium ore dust was added as well. Exposures were of the chronic type. (Chameaud et al. 1974, 1976, 1978).

The lungs of about four hundred of eight hundred rats were examined both grossly and microscopically. A total of 250 benign and malignant tumors were found! In addition, two types of metaplasia were present, one in the alveoli, the other in the bronchioles. Adenocarcinomas appeared that were invasive, although limited to the lung. Furthermore, there were tumors at relatively low exposures (500 WLM) relative to the PNL life-span studies and Rochester findings, although the maximum incidence appeared at 9,600 WLM (96 days at 5 hr/day with 20% to 30% daughter products). There were fewer tumors at 14,000 WLM and none at 21,000 WLM or in the controls. There were more carcinomas or adenocarcinomas in the range of 4,500 to 9,600 WLM, more adenomas in the lower brackets, and a maximal number of epidermoid carcinomas at 9,600 WLM. There was also an optimal exposure rate and a progression in both lesion type and latent period with dose and dose rate.

The addition of stable cerium advanced by up to three months the appearance of cancers induced by radon daughters. By contrast, uranium ore dust seemed to have little influence.

The effect of adding tobacco smoke was found to depend on the temporal sequence of exposures to it and to radon daughters. When exposure to tobacco smoke followed all of the exposures to radon daughters, the total tumor yield was greater than that produced by radon daughters alone. When smoking occurred first, there was no change in the tumor yield produced by radon daughters alone (Chameaud et al. 1981). These findings contrast to those found in dogs at PNL (see section 2 above), where the tobacco smoke and radon daughter exposures were alternated and given in the same day. Yet, on the whole, the researchers at CEA and PNL find more similarities than differences between each other and between animals and man.

There is no question that the French and PNL experiments make the rat look more like man than any other test animal. Yet, earlier work with the rat (e.g., at Rochester), which involved both standard rats and specific pathogen-free animals of the same strain, showed much lower incidence of lung tumors.

4. Commentary on the Animal Research

More experimental work needs to be done that can explain the differences in results among the various laboratories or between animals and man.^(a) These

(a) A cogent summary of the dilemmas in the radon work and evidence of strong carcinogenic action of other inhaled radionuclides are found in the paper by Bair (1970) at the Gatlinburg symposium in 1969 and in ICRP Publication 31 (1980).

differences appear to reside primarily in tumorigenesis. Metabolic effects and most other pathology seem to be much more uniform among laboratories and species for a given set of exposure conditions. We know that inbred strains of animals from the same original stock can show marked individual differences after a few generations in a new location. We know also that many subtle differences appear at the cellular level, e.g., in tissue cultures, in different laboratories. All we can conclude is that our knowledge is far from complete. The idea of unknown endogenous or exogenous cofactors for carcinogenesis remains an attractive avenue of thought.^(a)

Despite the differences among laboratories and apparently between man and the animal models, there is no question that the animal work has been very useful, particularly for establishing effects over a very wide range of doses and, of course, for pathologic and physiologic responses and for dosimetry data as described in section V. Observations in animals not unequivocally demonstrated in man include an increase in tumor production with increase in the unattached fraction of radon daughters and in disequilibrium and the importance of temporal sequence of exposure in developing effects of cigarette smoke and radon daughters. However, these may not be real differences. Only further investigation can decide these points.

IX. Research on Control of the Mine Environment

Most of the efforts to control exposures in the mines have been engineering projects. Yet, the biomedical community got involved, partly because many of the personnel from PHS and a few of the AEC personnel concerned were industrial engineers or industrial hygienists. They got involved in advising on ventilation and measuring its effectiveness. They also got involved in measures to seal the rock formations to prevent egress of radon.

Perhaps the areas of most pertinence to this review of internal emitter toxicology are instrument design, aerosol research, and respirators.

A. Instrument Design

Many of those connected with research on radioactivity were either physicists or were otherwise versed in electronics and had already developed instrumentation for their own programs. They saw the needs and sometimes teamed up with instrument manufacturers to design and provide equipment for the rapid measurement of radon daughters and thus of the working level. Other individuals and groups got involved in exploration of the utility of whole-body counters to measure residual radioactivity from radon progeny. The AEC supported development of surveillance monitoring equipment at the Health and Safety Laboratory (HASL) in New York, at MIT (simultaneous detection of radon gas and radon daughters), Idaho Operations Office, Colorado State University, the Eberline Instrument Corporation, the General Electric Company, and others. The Public Health Service brought in its regional laboratories.

(a) When we review the genesis of lung cancer by plutonium in chapter 9 we will see what appears to be the inverse of the interspecies relationship with radon.

Devices for air characterization were built along two distinct lines, those intended for sampling of a general area with considerable sensitivity and devices to be worn on the person to give useful, but not highly accurate, readings. The "Instant Working Level Meter" from MIT (Groer, Evans, and Gordon 1973) is a good example of the former; it could evaluate the working levels present in about four minutes.

B. Aerosol Research^(a)

Aerosol research was most active at Rochester (basic work), Los Alamos (filters, absorbers, particle-size characterization), HASL (mixture of basic and applied), PNL (air cleaning methods), Colorado State (characterization), the Bureau of Mines (applied studies), and at some of the centers abroad.

C. Respirators

Development of respirators, which at long last the miners were persuaded to wear, was concentrated by tradition in the Bureau of Mines and the manufacturers of industrial hygiene equipment. However, the Colorado State University group had a contract for evaluation of respiratory protective equipment, PNL worked on a respirator using electrostatic precipitation, and several laboratories with good respiratory physiologists were invited to participate in the AEC-sponsored conferences on respirators. As always, the chief problem with respirators was the weight of those with a full face mask and supplied air, and the fit without leaks of the lighter, simpler devices, which filter out the dust and thereby the attached daughters.

D. Bioassay

A final area associated with control is bioassay. We have already referred to measurement of ^{210}Po or ^{214}Bi in urine. This was extended by Stuart Black of the PHS from the miners to measuring radium daughters excreted by mules that had worked in the mines. The mule, being larger than man, would put out more activity and thus be further above the sensitivity threshold of the methods.

Probably the most useful measurement has been the in-vivo counting of bodily deposits with a variety of whole-body and partial-body counters.

In general, bioassay has not played a central role in evaluating the exposures of miners to radon or its progeny.

X. Environmental and Population Exposures to Radon and Radon Daughters

We have had little to say so far about environmental and population exposures from radioisotopes. Most of our discussion of these will come when we review the entire field in chapters 11 through 15. However, recent keen interest in possible health effects from radon and daughters in the environment^(b) has both stimulated new work and motivated reviews and interpretation of much work already done. It is so closely related to other sections of this review of the radon and uranium miner saga that it should be considered now, rather than waiting for the fuller discussion of environmental work.

(a) Considered in more detail in chapter 9.

(b) This interest is much broader than that around the spas discussed earlier.

Pre-World-War-II studies were made by the Rajewsky group from Frankfurt and by others of the radon concentrations in air and water of central Europe. Interest in such figures was part of a general effort to determine levels of natural background radiation and their possible significance. Newer work has developed around the possibilities of significant radon and daughter exposures in dwellings and workplaces. This work is very fully summarized in the UNSCEAR (1977) report and in two reports from the National Council on Radiation Protection and Measurements (NCRP 1975, 1984b). It is a very active field at present with a section in a special report due very soon from the National Research Council, a summary in the U.K. Radiation Protection Bulletin (Cliff 1978), communiques from the Environmental Protection Agency, etc. This enterprise has required the attention of many researchers in a few centers active in radiation toxicology. While the early work was primarily European, much of the later work has been American.

A. Exposures Indoors

The pioneer in indicating that people who live in stone or brick houses are in an environment of higher radioactivity than those who live in wooden houses was a Swedish student named Hultqvist (1956). He wrote a thesis on measurements of both airborne radioactivity and the relative gamma-ray fluxes in houses and other buildings as a function of the type of building materials used. This was followed by work primarily out of Argonne National Laboratory, the AEC's Health and Safety Laboratory in New York, and New York University. Levels of both radon and thoron and their progeny were determined under a great variety of conditions, as summarized in UNSCEAR (1977) and NCRP (1975).

The big "flap" came about 1966 when it was realized that tailings from uranium mills had been used as fill dirt or for other purposes in the construction of new homes in Grand Junction and Durango, Colorado. The Public Health Service, assisted by AEC personnel, surveyed several thousand homes and decided that about 20% needed remedial action. The prime source was soil under or around the house. The radon levels presented no immediate threat to health. However, in view of the fact that residents occupied the houses approximately 80% of the time (the other 20% they were outdoors), and because of the presence of small children, and the strong reaction of the populace, drastic action was taken. Many houses essentially had their foundation soils removed and replaced at government expense. Even some streets were redone.

The Surgeon General issued guidelines in the 1972 *Code of Federal Regulations*, which recommended remedial action above 0.05 WL, and possible suggested action between 0.01 and 0.05 WL. Many researchers were pressed into service to help make the measurements and interpret them.

A somewhat similar situation was found to prevail in parts of Florida, where phosphate mining was active. The rock formations that were high in phosphate happened also to be rather rich in uranium, and thus the other members of the decay chain. Again, houses were built on land prepared in part from the tailings of the phosphate extraction processes. In both Florida and in Tennessee, where similar phosphate rock mining took place, levels of radon on the order of 1,000 pCi/m³ were found.^(a) This problem led to a request to the NCRP from the

(a) Note that these environmental levels for air are given as *per cubic meter* rather than *per liter*.

governor of Florida and elicited not only a specific response, but a more wide-ranging report, which considered the entire uranium series (NCRP 1984b).

With the energy crunch, still another facet of radon exposure indoors has become active. As houses are being built tighter, and older ones made tight, the air turnover within has been reduced. Measurements indicate that there can be significant increases in radon and radon daughter levels. Is it significant or potentially significant biologically? Cliff (1978) reasons that 90% of lung cancers are due to smoking and that it is unlikely that more than 10% of the remaining cases could be due to radon daughter exposure, i.e., 1% of the total at the levels now extant in U.K. housing. However, he points out that Sweden already has legislation to limit air leakage in homes to less than 0.5 room air changes per hour in winter. The U.K. might go even further. If they should go to 0.2 room air changes per hour, the annual mean population exposure could rise markedly, e.g., 0.78 WLM. This would bring population exposures well above the customary factor of ten to thirty below occupational exposure.

A further consideration is the fact that the indoor exposure conditions favor greater effectiveness of the aerosols. The fraction of unattached ^{218}Po (RaA) is greater, the exposure is greater, the exposure is essentially continuous, and the particle size distribution favors the smaller sizes with greater retention in the respiratory tract.

The NCRP report shows indoor radon concentrations from about 50 pCi/m³ and 70 pCi/m³ in office buildings and wood frame homes in Massachusetts to 1,300 and 1,400 pCi/m³ in Florida and Tennessee phosphate rock mining areas. These are mean figures with a log-normal distribution. Figure 3.7 shows a probit plot from work of George and Breslin (1980) for radon concentrations in picocuries per liter outdoors, on the first floor, and in the cellar of typical buildings in New York. Figure 3.8 illustrates the daughter concentrations in the same manner expressed as annual mean working levels.

These are normal buildings standing in granitic rock or detritus therefrom with normal uranium concentrations. While the means are not high enough to cause immediate concern, they point toward a possibly significant role in inducing lung cancer in some of the extreme cases. This becomes more impressive when one examines the dose equivalent rates to lung or portions thereof, from a number of naturally occurring radionuclides (NCRP 1975, table 29). The dose from 150 pCi/m³ of ^{218}Po (or ^{214}Po) to the segmental bronchioles is by far the highest of all natural radioisotopes at levels of intake consistent with measured exposures.

The more recent NCRP report (1984b) updates the findings, particularly as they apply to the indoor environment. It concludes that under the "right" circumstances, indoor radon and daughters can constitute a major portion of the radiation dose to man from natural sources. The report suggests methods for remedial action and that these be instituted when total exposure to radon daughters for an individual in the population exceeds an annual average of 2 WLM including background. This equates to about 0.04 WL on the average. This is half of the level applied for occupational exposure and represents the first time it has been necessary to set a population level at more than one-tenth of the occupational level. Avoiding this by recommending remedial action at a lower level was considered to involve unacceptable expense and hardship. Also, the total number of cases near or above the limit is probably small.

There is no doubt that some of the hysteria of the general public concerning radiation is showing through in the urgency attached to this work. Yet, if we

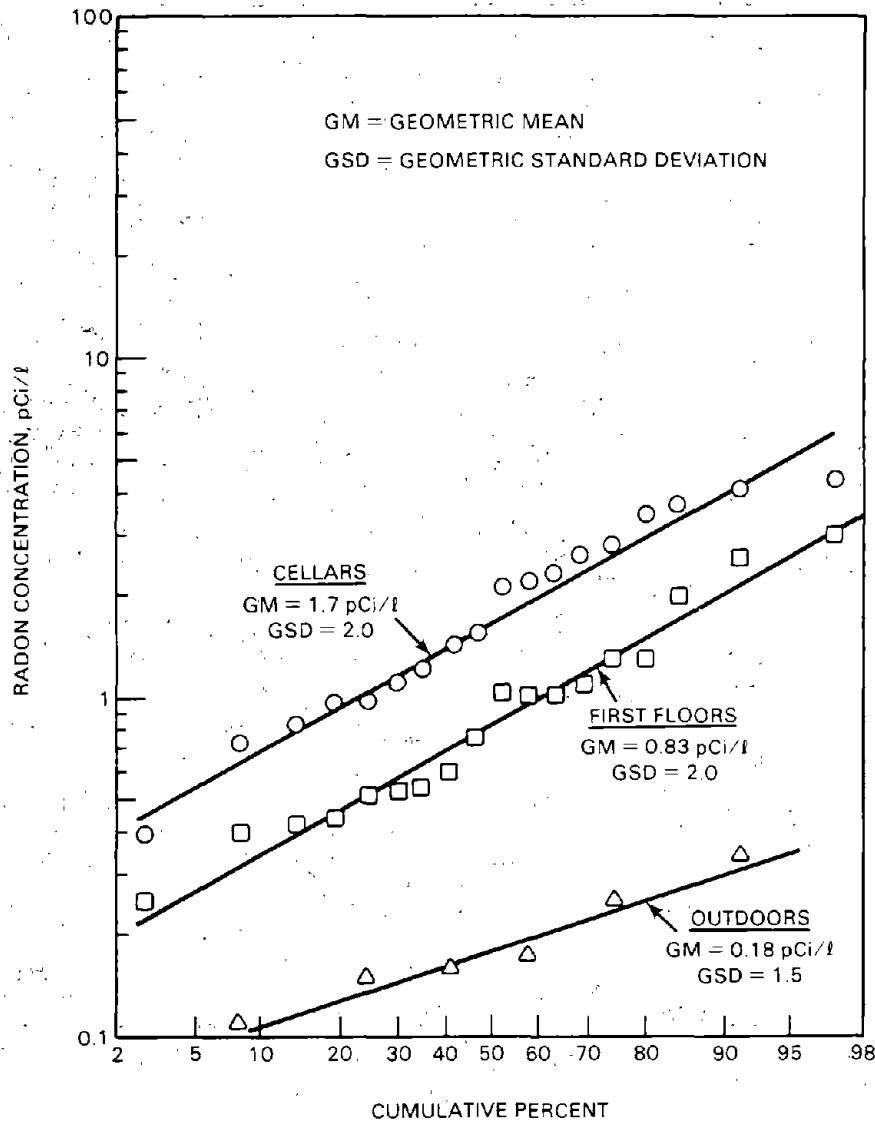


FIGURE 3.7. Distribution of annual mean radon concentrations in a few New York buildings. (Redrawn from George and Breslin 1980.)

add some extra radon released from water used for showering, particularly in areas of high natural radon water, a tight house built of granite with more than average uranium content, with perhaps 0.5 room air changes per hour, we are moving clearly toward levels of potential biological significance. This work will undoubtedly continue unless world events occur that make worrying over such relatively minor matters unimportant. The literature is growing rapidly already.

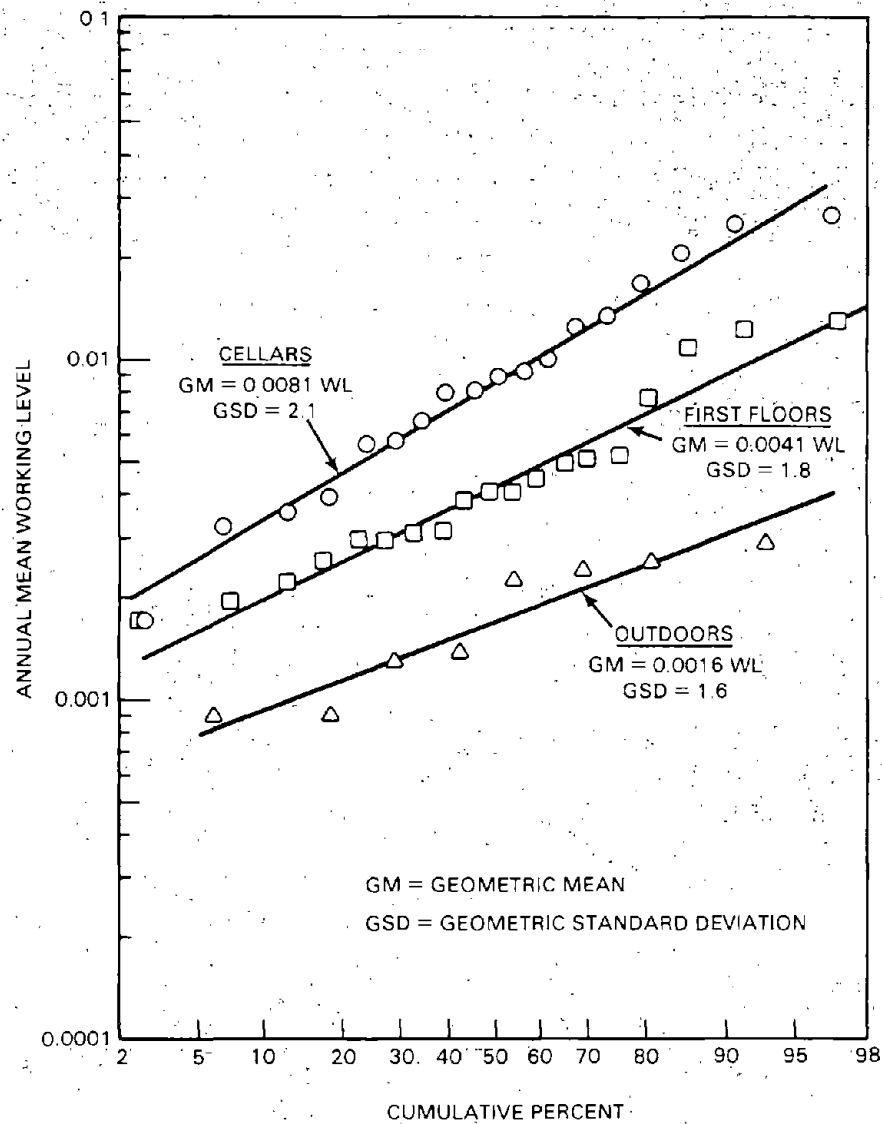


FIGURE 3.8. Distributions of annual mean working levels in the same New York buildings. (Redrawn from George and Breslin 1980.)

Table 3.6 places the figures we have been reviewing in perspective by using representative average exposures (Wrenn 1981).

Currently, the mean population exposures indoors are a comfortable margin below those in the uranium mines. But remember that the uranium miners' got lung cancer down to about 60 CWLM. Thus, the margin of safety is not as comfortably large as we used to think it was.

TABLE 3.6. Representative Exposures to Radon-222 Progeny

Subjects or Location	WLa	WLMa,b
Uranium miners ^c	1-20	100-10,000
Outdoors	<0.001	—
Indoors	<0.01	10

^a To nearest order of magnitude.

^b Lifetime or duration of exposure.

^c Includes exposure before mid-1960s.

Source: Reset from Wrenn 1981.

The companion NCRP report already discussed (NCRP 1984a), addresses a wider range of biological problems with radon and its daughter products. These include dosimetry in an environmental atmosphere, in uranium mines, the experimental work with animals, and the all-important epidemiologic studies of the miners. The latter do not extend to the low-level exposures in buildings, of course, since that problem is too new.

B. Exposures Outdoors

The figures in table 3.6 for representative exposures to ²²²Rn progeny indicate a factor of ten difference in working level between indoors and outdoors. Although there are many and sometimes quite large variations in these values, in general the mean concentration of radon outdoors, either measured directly or inferred from daughter measurements, is about this factor lower than that indoors. However, the ranges may overlap. Work worldwide supports these conclusions.

The airborne radon and daughters from sources such as a uranium tailings pile became a source of considerable concern beginning in the 1960s. Concentrations of airborne uranium, radium, and radon were measured. None were of immediate dosimetric significance. Those from uranium mill tailings did not carry very far, falling by a factor of ten in 1 km. Water can carry the radium and radon much farther (more in chapter 11).^(a)

Much of interest to meteorologists has come out of these widespread measurements, but that is beyond our scope for now.

(a) Recently, there have been measurements of radon and radon daughter levels in caverns frequented by the public. An example is work in Howe Caverns by Seymore, Ryan, and Corelli (1980) at Rensselaer Polytechnic Institute in Troy, New York. The levels ranged from 0.008 to 0.25 WL with radon concentrations from less than 1 to 32 pCi/l. Since neither the public nor employees are in the cavern for extended periods, these levels were considered of no health concern.

C. Amounts in Water

Hursh et al. (1965) quote measurements of radon in natural waters from various parts of the world. Whereas the averages ranged from about 2 pCi/l to 30,000 pCi/l, with one very high value for springs in Beshtaugorsky, USSR (228,000 pCi/l), the maxima sometimes exceeded the average by factors approaching ten. It is interesting that natural waters with high ^{226}Ra content did not always have correspondingly high radon contents and vice versa. Thus, expected radon content cannot be arrived at by calculation from the radium content of water.

UNSCEAR (1977) reports that radon concentration in water used from private and communal wells frequently exceeds 20 pCi/l, and as much as 1,000 pCi/l is not uncommon. Water from thermal springs like Badgastein (see section VIII) may average 40 nCi/l (40,000 pCi/l). Open-air radon concentrations of about 1 pCi/l and indoors of about 10 pCi/l may arise from use of such water. When we remember that the original occupational standard for radon was 10 pCi/l, these values are not trivial, especially if there are other carcinogens in the environment.

D. Significance

UNSCEAR concludes that absorbed doses arising from inhalation of radon decay products under average natural conditions may be 160 mrad/yr to the segmental bronchioles, 30 mrad/yr to the whole lung, plus another 30 mrad/yr to terminal bronchioles, and 4 mrad/yr to the whole lung from the decay products of thoron. The total annual exposure of lung from all sources, both external and internal, is about 110 mrad/yr. The contribution of the radon daughters is thus over a quarter of the total, perhaps a third in some instances. In the case of the tracheobronchial tree, the total dose from natural background sources is about 200 mrad/yr, of which a substantial portion, on the average, is due to radon daughters. Thus, in terms of finding the contribution to dose, the work on naturally occurring levels of radon and radon daughters has been well worth doing. At present, we do not attach major biological significance to these doses and dose rates. The interpretation depends upon the models chosen for dose-effect relationships. However, they are close enough to significance over the lifetime of man to make us glad that we know approximately what they are. They are neither so trivial that they can be neglected, nor of clearly demonstrable biological significance. More studies are clearly needed.

E. Recent Events

Recently, an entire issue of the journal *Health Physics* was devoted to a series of papers on the measurement and possible significance of exposure to radon and its daughters indoors (Nero and Lowder 1983). The contents of this issue are given as note 1 at the end of this chapter. The growing emphasis on population exposures to radon and radon daughters is evident in these and even more recent publications.

The theme discussed above has been enlarged upon considerably in very recent symposia and publications. We have already encountered the "Specialist Meeting and Its Assessment of Radon and Daughter Exposure and Related Biological Effects" held in Rome in 1980 and whose proceedings were published in 1983. The table of contents of this symposium, note 2 to this chapter, shows the growing interest in indoor exposures to radon.

XI. Summary and Commentary

This chapter begins with the centuries-old malady afflicting certain miners in central Europe and ends with the present-day view that indoor concentrations of radon and its daughter products may constitute the largest single source of naturally occurring radiation.

Like radium, radon has been used for many years in therapy of cancer. This was accomplished by the preparation of radon "seeds" that could be placed close to an area, usually cancerous, requiring treatment. As with radium, it was the penetrating "hard" radiation that was important. In this case, it came from some of the decay products of radon, not from radon itself, which is an alpha-particle emitter. Also, like radium, radon has been used internally as a therapeutic nostrum for its alleged "stimulative" effects on various body processes. For this, the primary sources have been the large therapeutic spas. True benefits from these are hard to prove. True benefits from radon seeds are well known.

Our principal consideration is again the untoward effects of this naturally occurring series of radionuclides. In the mining of uranium, there is always radium present and thus radon and its daughter products. The tortuous path from complete mystery to a proven relationship between radon-plus-daughter-product exposure of uranium miners and lung cancer is a central theme of this chapter. The problem of the uranium miners is, of course, not uranium at all; it is principally the daughter products of radon. The proper characterization of the role of the daughter products has added further complexity to the already complex problem of bringing causation to the door of radon. The chapter reviews these in some depth.

The epidemiology of uranium miner populations began in the central European mines but did not become acceptable until relatively recently. We review this epidemiology with special emphasis on the work done in the Colorado Plateau area of the United States, the studies in Czechoslovakia, and, to a lesser extent, Canada, Sweden, etc. A central problem to the epidemiology has been dosimetry. The problems of establishing the radiation dose from radon and its progeny have been much more severe than in the case of radium. They even required the devising of a special unit—the working level and its time derivatives, working level month and working level year. The genesis of these units, their need, utility, and problems are reviewed in the chapter.

No institution can be singled out as being a mecca for dosimetric and epidemiologic studies with radon. In the United States, the U.S. Public Health Service, the state health departments, the AEC's Health and Safety Laboratory, and scattered university groups played central roles, primarily in the study of the miners and their environment.

As with radium and uranium, a large experimental program with animals was needed to complement and supplement the efforts surrounding human exposures. Centers for this work have been the groups at the University of Rochester Atomic Energy Project, Pacific Northwest Laboratory, and, to a lesser extent, Argonne National Laboratory. In Europe, much experimental work was done in France and Germany; the work extending back many decades in Germany. There have appeared to be many puzzling differences between the results of animal experiments and the findings in the uranium miners. Most of these have now been explained, or new, less-conflicting data have been gathered by better techniques and with better animal strains and husbandry. Yet, it still seems clear that something is different between the animal exposure situations and mining

(or milling) experience. Part of it may be due to secondary agents in the mine atmospheres. The work at Pacific Northwest Laboratory concentrated on adding adjuvants such as cigarette smoke, uranium ore dust, diesel exhaust fumes, and the like. However, the results did not demonstrate effects as large as were necessary to explain the differences. We are thus left with the provisional conclusion that the mechanism, type, and site of origin of the lung cancers in man may be different from those in the animal populations studied. This may or may not be resolved in the future. Exposures of man are now drastically lower, and many fewer cancer cases attributable to mining may, fortunately, occur.

The spas and "therapeutic" mines are sources of interesting information, and this is reviewed. However, except for characterization of the concentrations of radionuclides present and the associated dosimetry, these studies have not yielded acceptable epidemiology that compares in any way with the careful and relatively extensive analyses of the populations of miners.

The current concerns about population exposure arose partly from the presence of mill tailings in construction materials, the location of phosphate mines in areas with high radium and radon contents of the strata, and the much tighter sealing of homes and buildings for energy conservation. These are discussed briefly. While currently something of a cause célèbre, the true distribution of unusually high air concentrations of radon, and its daughters indoors, the numbers of people exposed, and the possibility of significant biological effects must await more detailed work for a satisfactory evaluation.

Note 1—Table of Contents of Special Issue of *Health Physics* (vol. 45, no. 2, 1983) on Indoor Radon^(a)

Indoor Concentrations, Exposures and Risks

A. V. Nero: Indoor radiation exposures from ²²²Rn and its daughters: a view of the issue

Thomas F. Gesell: Background atmospheric ²²²Rn concentrations outdoors and indoors: a review

A. V. Nero: Airborne radionuclides and radiation in buildings: a review

K. D. Cliff, A. D. Wrixon, B. M. R. Green and J. C. H. Miles: Radon daughter exposures in the U.K.

F. Steinhäusler, W. Hofmann, E. Pohl and J. Pohl-Rüling: Radiation exposure of the respiratory tract and associated carcinogenic risk due to inhaled radon daughters

C. T. Hess, C. V. Weiffenbach and S. A. Norton: Environmental radon and cancer correlations in Maine

Source Characterization

Bernd Kahn, Geoffrey G. Eichholz and Frank J. Clarke: Search for building materials as sources of elevated radiation dose

John G. Ingersoll: A survey of radionuclide contents and radon emanation rates in building materials used in the U.S.

Niels Jonassen: On the determination of radon exhalation rates

Geordie H. Zapalac: A time-dependent method for characterizing the diffusion of ²²²Rn in concrete

G. Scicchetti, G. F. Clemente, G. Ingrao and F. Scacco: Results of a survey on radioactivity of building materials in Italy

(a) Nero and Lowder (1983).

Surveys of Radon and Radon Daughter Concentration Indoors

C. E. Roessler, G. S. Roessler and W. E. Bolch: Indoor radon progeny exposure in the Florida phosphate mining region: a review

A. C. George and J. Eng: Indoor radon measurements in New Jersey, New York and Pennsylvania

A. V. Nero, M. L. Boegel, C. D. Hollowell, J. G. Ingersoll and W. W. Nazaroff: Radon concentrations and infiltration rates measured in conventional and energy-efficient houses

Robert L. Fleischer, Antonio Mogro-Campero and Larry G. Turner: Indoor radon levels in the Northeastern U.S.: effects of energy efficiency in homes

A. C. George, E. O. Knutson and H. Franklin: Radon and radon daughter measurements in solar buildings

W. Chruscielewski, T. Domanski and W. Orzechowski: Concentrations of radon and its progeny in the rooms of Polish spas

Notes

H. Ward Alter and Richard A. Oswald: Results of indoor radon measurements using the Track Etch® method

Howard M. Prichard, Thomas F. Gesell, C. Thomas Hess, Conrad Weiffenbach and Philip Nyberg: Integrated radon data from dwellings in Maine and Texas

W. B. Johnson and P. G. Bailey: Study of radon daughter concentrations in Polk and Hillsborough counties

A. G. Scott: The distribution of average radon daughter concentrations in houses estimated from single-sample surveys

Investigations of Radon Daughter Behavior

A. C. George, E. O. Knutson and K. W. Tu: Radon daughter plateout—I. Measurements

E. O. Knutson, A. C. George, J. J. Frey and B. R. Koh: Radon daughter plateout—II. Prediction model

Gun Astri Swedjemark: The equilibrium factor F

S. N. Rudnick, W. C. Hinds, E. F. Maher and M. W. First: Effect of plateout, air motion and dust removal on radon decay product concentration in a simulated residence

Ronald C. Bruno: Verifying a model of radon decay product behavior indoors

A. G. Scott: Radon daughter deposition velocities estimated from field measurements

Niels Jonassen: The effect of electric fields on ^{222}Rn daughter products in indoor air

Measurement Techniques

Howard M. Prichard: A solvent extraction technique for the measurement of ^{222}Rn at ambient air concentrations

Bernard L. Cohen and Ernest S. Cohen: Theory and practice of radon monitoring with charcoal adsorption

K. L. Revzan and W. W. Nazaroff: A rapid spectroscopic technique for determining the potential α -energy concentration of radon decay products

W. W. Nazaroff, F. J. Offermann and A. W. Robb: Automated system for measuring air-exchange rate and radon concentration in houses

Notes

Philip C. Nyberg and David E. Bernhardt: Measurement of time-integrated radon concentrations in residences

Stephen W. Skinner and Philip C. Nyberg: Method for the calculation of radon response characteristics of integrating detectors

J. G. Ingersoll, B. D. Stitt and G. H. Zapalac: A fast and accurate method for measuring radon exhalation rates from building materials

Isabel M. Fisenne, Andreas George and Mark McGahan: Radon measurement intercomparisons

J. P. McLaughlin and N. Jonassen: The intercalibration of a radon daughter detection system with a radon detection system

R. A. Washington and W. J. Courneya: The measurement of low concentrations of radon in air

Note 2—Contents of the Proceedings of a Special Meeting (1980) on the Assessment of Radon and Daughter Exposure and Related Biological Effects^(a)

I. INTRODUCTORY PAPER

NEA Program of Work on Radon and Radon Daughter Dosimetry and Monitoring
P. J. RAFFERTY

PLENARY DISCUSSION: Administrative Aspects of the Problem and the Role of International Organizations

II. MEASUREMENT TECHNIQUES

Measurement of Exposure to Radon and Its Progeny Using Kodak LR-115 Type II Foil: I. Laboratory Investigations of the Detector Response
W. ORZECOWSKI ET AL.

Measurement of Exposure to Radon and Its Progeny Using Kodak LR-115 Type II Foil: II. Calibration of the Detector
W. CHRUSCIELEWSKI ET AL.

A Passive Integrating Method of Measuring Relative Radon and Thoron Exhalation Rates
J. P. McLAUGHLIN

Size Characterization of Alpha-Emitting Aerosols by Means of an Inertial Spectrometer and Track-Etching Detectors
V. PRODI ET AL.

Measurement of Radon and Radon Daughters
N. JONASSEN

Automated Measurements of Rn-222 Daughter Concentrations with the Environmental Working Level Monitor
P. G. GROER ET AL.

Measurement of Environmental Radon-222 in Selected Areas of Taiwan
T. Y. CHANG MEI AND P. S. WENG

III. DOSIMETRY

Problems of Lung Dosimetry Due to Inhaled Radon Decay Products in Relation to Epidemiological Studies
W. HOFMANN AND F. STEINHAÜSLER

Dose Distribution in the Human Organism Due to Incorporation of Radon and Decay Products as a Base for Epidemiological Studies
E. POHL AND J. POHL-RÜLING

(a) Clemente et al. (1982).

Uranium and Thorium Isotopes in Uranium Miners' Lungs
N. P. SINGH ET AL.

PLENARY DISCUSSION: Physical Dosimetry and Its Relevance to Biology

IV. POPULATION EXPOSURE

Radon and Radon Daughter Measurements in Dwellings
C. SAMUELSSON AND G. JONSSON

Radioactivity in Houses Built of Aerated Concrete Based on Alum Shale
G. A. SWEDJEMARK

Assessment of Radon in Norwegian Dwellings
E. STRANDEN

Exposure to Radon-Daughters in Dwellings
A. WICKE AND J. PORSTENDORFER

Radon Daughter Exposures in Energy-Efficient Buildings
A. V. NERP ET AL.

Preliminary Assessment of Occupational Radon Dosimetry in the Araxá Fe-Nb Facility
A. S. PASCHOA AND E. PALACIOS

Radon in Finnish Dwellings: Aspects of Epidemiological Studies and Radiation Protection
O. CASTREN

Evaluation of the Radon and Radon Daughter Exposure in the Italian Population
G. SCIOCCHETTI ET AL.

The Assessment of Indoor Exposure From Gamma Emitters and Radon in Poland
B. J. GWIAZDOWSKI ET AL.

V. BIOLOGICAL EFFECTS AND RISK ASSESSMENT

Influence of Radon Daughter Exposure Rate and Uranium Ore Dust Concentration on Occurrence of Lung Tumors
F. T. CROSS ET AL.

Cancers Induced by Rn-222 in the Rat
J. CHAMEAUD ET AL.

An Epidemiological Study of Chromosome Aberrations in a Radon Spa
J. POHL-RÜLING AND P. FISCHER

Epidemiological Implications of Radon in Public Water Supplies
T. F. GESELL ET AL.

Mortality and Indoor Daughter Concentrations in 13 Canadian Cities
E. G. LETOURNEAU AND D. T. WIGLE

Estimating Population Health Risk from Low-Level Environmental Radon
D. R. FISHER

On the Suitability of Epidemiological Studies of Population Groups Exposed to Elevated Levels of Radon and Daughters
F. STEINHÄUSLER ET AL.

PLENARY DISCUSSION: The Need for an International Radon Epidemiology Program

VI. CONCLUSIONS OF THE MEETING

Recommendations and Conclusions

Appendix A: List of Participants

Appendix B: Summary of Subsequent Meeting of NEA Group of Experts on Radon Dosimetry and Monitoring, Paris, April 1980.

References

- Altshuler, B., N. Nelson, and M. Kuschner. 1964. Estimation of lung tissue dose from the inhalation of radon and daughters. *Health Phys.* 10:1137-61.
- Andreev, S. V. 1984. *Balneotechnische, stahlenhygienische und dosimetrische Aspekte der Radon-therapie in der USSR*. Paper presented at an international symposium held at Bad Munster am Stein-Edernborg, Demeter Verlag, catalog no. B 3642 F. *Z. Phys. Med. Baln. Med. Klim (Sonderheft 1)* 13:32-39.
- Andrews, J. N. and D. F. Wood. 1974. Radium-226, radium-222 and lead-210 in bath thermal springs compared with some environmental waters. *Health Phys.* 27:307-10.
- Archer, V. E. 1979. Factors in exposure-response relationships of radon daughter injury. In *Lung cancer epidemiology and industrial applications of sputum cytology*, pp. 324-67. Proceedings of a conference/workshop held in Golden, Colo. Golden, Colo.: Colorado School of Mines Press.
- Archer, V. E. 1981. Perspective on cancer and radon daughters. In Gomez 1981, pp. 811-15.
- Archer, V. E., J. K. Wagoner, and F. E. Lundin. 1973. Lung cancer among uranium miners in the United States. *Health Phys.* 25:351-71.
- Archer, V. E., B. E. Carrol, H. P. Brinton, and G. Saccomanno. 1964. Epidemiological studies of some non-fatal effects of uranium mining. In *Radiological health and safety in mining and milling of nuclear materials*, vol. 1, pp. 21-36. Proceedings of a symposium held in Vienna, August 26-31, 1963. Vienna: International Atomic Energy Agency.
- Aurand, K., W. Jacobi, and H. Schraub. 1956. Untersuchungen über die folgenprodukte des Radons in Gasteiner Thermalwasser. Reprint from *Osterreichischen Akademie der Wissenschaften*, Vienna.
- Aurand, K., W. Jacobi, H. Muth, and A. Schraub. 1960. Weitere Untersuchungen zur biologischen Wirkung des Radons und seiner Folgeprodukte. *Strahlentherapie* 112:262-72.
- Bair, W. J. 1970. Inhalation of radionuclides and carcinogenesis. In *Inhalation carcinogenesis*, eds. M. G. Hanna, Jr., P. Nettesheim, and J. R. Gilbert, pp. 77-101. Proceedings of a conference held in Gatlinburg, Tenn., October 8-11, 1969. Springfield, Va.: National Bureau of Standards, U.S. Department of Commerce.
- Bair, W. J. 1986. Experimental carcinogenesis in the respiratory tract. In *Radiation carcinogenesis*, eds. A. C. Upton, R. E. Albert, F. J. Burns, R. E. Shore, pp. 151-67. New York: Elsevier Press.
- Bale, W. F. 1944. Letter to J. J. Nickson at Metallurgical Laboratory in Chicago, September 22, 1944.
- Bale, W. F. 1951. *Memorandum to the files, March 14, 1951: Hazards associated with radon and thoron*. Washington, D.C.: U.S. Atomic Energy Commission, Div. of Biology and Medicine. [Reprinted as Bale 1980.]
- Bale, W. F. 1980. *Hazards associated with radon and thoron*. Memorandum to the files, March 14, 1951. Reprinted as a landmark paper with comments by J. N. Stannard in *Health Phys.* 38:1061-66.
- Bale, W. F. and J. V. Shapiro. 1956. Radiation dosage to lungs from radon and its daughter products. In *Proceedings of the international conference on the peaceful uses of atomic energy*, vol. 13, pp. 233-36. Held in Geneva, August 8-20, 1955, New York: United Nations.
- Běhounek, F. 1936. Zwei neue Apparate zur unmittelbaren Bestimmung des in Wasser und in Luft enthaltenen Radons. *Physik. Z.* 37:203-08.
- BEIR. See Biological Effects of Ionizing Radiation III.
- Bell, R. F. and J. C. Gilliland. 1964. Urinary lead-210 as index of mine radon exposure. In *Radiological health and safety in mining and milling of nuclear materials*, vol. 2, pp. 411-23. Proceedings of a symposium held in Vienna, August 26-31, 1963. Vienna: International Atomic Energy Agency.
- Biological Effects of Ionizing Radiation III. 1980. *The effects on populations of exposure to low levels of ionizing radiation*. Committee on the Biological Effects of Ionizing Radiations; National Research Council. Washington, D.C.: National Academy Press.

- Bouchard, C. and V. Balthazard. 1906. Action toxique et localisation de l'émanation du radium. *C. R. Hebd. Séances Acad. Sci.* 143:198-200.
- Bouchard, C., P. Curie, and V. Balthazard. 1904. Action physiologique de l'émanation du radium. *C. R. Hebd. Séances Acad. Sci.* 138:1384-87.
- Brüyn, K. 1955. *Uranium country*. Boulder, Colo.: Univ. of Colo. Press.
- Casarett, G. W. 1952. *Histopathology of alpha radiation from internally administered polonium*. UR-201. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Chamberlain, A. C. and E. D. Dyson. 1956. The dose to the trachea and bronchi from the decay products of radon and thoron. *Br. J. Radiol.* 29:317-25.
- Chameaud, J., R. Perraud, J. Crétien, R. Masse, and J. Lafuma. 1978. Experimental study of the combined effect of cigarette smoke and an active burden of radon-222. In *Late biological effects of ionizing radiation*, STI/PUB/489, vol. 2, pp. 429-36. Proceedings of a symposium held in Vienna, March 13-17, 1978. Vienna: International Atomic Energy Agency.
- Chameaud, J., R. Perraud, J. Lafuma, R. Masse, and J. Pradel. 1974. Lesions and lung cancers induced in rats by inhaled radon 222 at various equilibriums with radon daughters. In *Experimental lung cancer: Carcinogenesis and bioassays*, eds. E. Karbe and J. F. Park, pp. 411-21. Proceedings of a symposium held in Seattle, June 23-26, 1974. New York: Springer-Verlag.
- Chameaud, J., R. Perraud, R. Masse, and J. Lafuma. 1981. Contribution of animal experimentation to the interpretation of human epidemiological data. In Gomez 1981, pp. 222-27.
- Chameaud, J., R. Perraud, R. Masse, J. C. Nénot, and J. Lafuma. 1976. Lung cancer induced in rats by radon and its daughter nuclides at different concentrations. In *Biological and environmental effects of low-level radiation*, STI/PUB/409, vol. 2, pp. 223-28. Proceedings of a symposium held in Chicago, November 3-7, 1975. Vienna: International Atomic Energy Agency.
- Clemente, G. F., A. V. Nero, F. Steinhäusler, and M. E. Wrenn, eds. 1982. *Assessment of radon and daughter exposure and related biological effects*. Proceedings of the specialist meeting held in Rome, March 3-8, 1980. Salt Lake City: RD Press.
- Clemente, G. F., A. Renzetti, G. Santori, F. Steinhäusler, and J. Pohl-Rüling. 1984. Relationship between the ^{210}Pb content of teeth and exposure to Rn and Rn daughters. *Health Phys.* 47:253-62. [See also Clemente et al. 1982.]
- Cliff, K. D. 1978. Population exposure to the short-lived daughters of radon-222 in Great Britain. In *Radiological Protection Bulletin*, no. 22, January 1978. United Kingdom: National Radiological Protection Board.
- Cohn, S. H., R. K. Skow, and J. K. Gong. 1953. Radon inhalation studies in rats. *Arch. Ind. Hyg. Occup. Med.* 7:508-15.
- Cross, F. T. 1984. A review of radon inhalation studies in animals with reference to epidemiological data. Appendix C in *Assessment of the scientific basis for existing federal limitations on radiation exposure to underground uranium miners*. Prepared for the American Mining Congress, Senes Consultants Ltd., Willowdale, Ontario, Canada.
- Cross, F. T., W. J. Bair, W. J. Clarke, and J. M. Nielsen. 1968. *Project development report on uranium mining radiation hazards*. Ad Hoc Task Force on Uranium Miners, BNWL-CC-1613. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Cross, F. T., C. H. Bloomster, P. L. Hendrickson, and I. C. Nelson with B. L. Hooper, J. A. Merrill, and B. O. Stuart. 1974. *Evaluation of methods for setting occupational health standards for uranium miners*. A research report for the National Institute for Occupational Safety and Health. Richland, Wash.: Pacific Northwest Laboratory.
- Cross, F. T., R. F. Palmer, R. H. Busch, and R. L. Buschbom. 1982. Influence of radon daughter exposure rate and uranium ore dust concentration on occurrence of lung tumors. In Clemente et al. 1982, pp. 189-97.
- Cross, F. T., R. F. Palmer, R. H. Busch, G. E. Dagle, R. E. Filipy, and H. A. Ragan. 1986. An overview of the PNL radon experiments with reference to epidemiological data. In *Life-span radiation effects studies in animals: What can they tell us?* CONF-830951, eds. R. C. Thompson and J. A. Mahaffey, pp. 608-23. Proceedings of the 22d annual Hanford life sciences symposium held in Richland, Wash., September 27-29, 1983. Springfield, Va.: National Technical Information Service.

- Cross, F. T., R. F. Palmer, R. E. Filipy, R. H. Busch, and B. O. Stuart. 1978. *Study of the combined effects of smoking and inhalation of uranium ore dust, radon daughters and diesel oil exhaust fumes in hamsters and dogs*. Final report to National Institute of Environmental Health Sciences, PNL-2744. Richland, Wash.: Pacific Northwest Laboratory.
- Desrosiers, A., A. Kennedy, and J. B. Little. 1978. ^{222}Rn daughter dosimetry in the Syrian golden hamster lung. *Health Phys.* 35:607-23.
- Djurić, D., D. Panov, M. Kilibarda, L. Novak, and M. Vukotić. 1964. Polonium in the urine of miners as a measure of exposure to radon: In *Radiological health and safety in mining and milling of nuclear materials*, vol. 2, pp. 431-41. Proceedings of a symposium held in Vienna, August 26-31, 1963. Vienna: International Atomic Energy Agency.
- Evans, R. D. 1935. Apparatus for the determination of minute quantities of radium, radon and thoron in solids, liquids and gases. *Rev. Sci. Instrum.* 6:99-112.
- Evans, R. D. 1950. Quantitative aspects of radiation carcinogenesis in humans. *Acta Unionis Internationalis Contra Cancrum* 6:1229-37.
- Evans, R. D. 1969. Engineers' guide to the elementary behavior of radon daughters. *Health Phys.* 17:229-52.
- Evans, R. D. and C. Goodman. 1940. Determination of the thoron content of air and its bearing on lung cancer hazards in industry. *J. Ind. Hyg. Toxicol.* 22:89-99.
- Evans, R. D., J. H. Harley, W. Jacobi, A. S. McLean, W. A. Mills, and C. G. Stewart. 1981. Estimate of risk from environmental exposure to radon-222 and its decay products. *Nature* 290:98-100.
- Failla, G. 1942. Metallurgical Laboratory Report CH-1347, declassified 1948.
- Federal Radiation Council. 1967. *Guidance for the control of radiation hazards in uranium mining*. Staff report no. 8, revised.
- Federal Register. 1967. *Federal Radiation Council. Radiation protection guidance for federal agencies*. Memorandum for the President, dated July 21, 1967, issued August 1, 1967, pp. 11183-84.
- Federal Register. 1968. *Federal Radiation Council. Radiation protection guidance for federal agencies*. Memorandum for the President, dated December 27, 1968, issued January 15, 1969, p. 576.
- Federal Register. 1970. *Federal Radiation Council. Radiation protection guidance for federal agencies*. Memorandum for the President, dated December 1, 1970, issued December 15, 1970.
- Federal Register. 1971. *Environmental Protection Agency. Underground mining of uranium ore. Radiation protection guidance for federal agencies*. Dated May 19, 1971, issued May 25, 1971, pp. 9480-82.
- Findeisen, W. 1935. Über das Absentzen kleiner, in der Luft suspendierter Teilchen in menschlichen Lungen bei der Atmung. *Arch. Gesant Physiol. Mens. Tiere (Pflügers)* 236:367-79.
- Fisenne, I. M. and N. H. Harley. 1974. *Lung dose estimates from natural radioactivity measured in urban air*. HASL #TM 74-7.
- Fisher, D. R. 1982. Estimating population health risk from low-level environmental radon. In Clemente et al. 1982, pp. 252-58.
- FRC. See Federal Radiation Council.
- Friedell, H. L. 1944. Letter on air analysis for radon content to area engineer, Rochester Area of Manhattan District. Signed by Dr. Friedell as Executive Officer of the Medical Section. Dated October 13, 1944.
- Friedell, H. L. 1981. *An overview of research in radiation biology and protective measures in the Manhattan Project during the war years, 1942-46*. [Draft manuscript of book to be published under Dr. Friedell's authorship and kindly made available to this author by him.]
- George, A. C. and A. J. Breslin. 1980. The distribution of ambient radon and radon daughters in residential buildings in the New Jersey-New York area. In *Natural radiation environment. III*, eds. T. F. Gesell and W. M. Lowder, CONF-780422 (vol. 2), pp. 1272-92. Washington, D.C.: U.S. Department of Energy, Technical Information Service.

- Gesell, T. E., H. M. Pritchard, and C. T. Hess. 1982. Epidemiological implications of radon in public water supplies. In Clemente et al. 1982.
- Gol'dberg, S. V. 1904. *On the theory of physiological action of Becquerel rays*. Dissertation, St. Petersburg. [Cited by Kushneva 1962.]
- Gomez, M., ed. 1981. *Radiation hazards in mining: Control, measurement, and medical aspects*. Proceedings of an international conference held at the Colorado School of Mines, Golden, Colo., October 4-9, 1981. New York: Society of Mining Engineers, American Institute of Mining, Metallurgical, and Petroleum Engineers, Inc.
- Gormley, P. G. and M. Kennedy. 1948. Diffusion from a stream flowing through a cylindrical tube. *Proc. R. I. Acad. Section A* 52:163.
- Governors' Conference. 1961. *Governors' conference on health hazards of uranium mines*. Summary report PHS publ. no. 843. Washington, D.C.: U.S. Department of Health, Education and Welfare.
- Groer, P. G., R. D. Evans, and D. A. Gordon. 1973. An instant working level meter for uranium mines. *Health Phys.* 24:387-95.
- Hannau, H. W. (undated). *Badgastein, the springs of eternal youth*. Garden City, N.Y.: Doubleday and Co.
- Harley, J. H. 1953. Sampling and measurement of airborne daughter products of radon. *Nucleonics* 11(7):12-15. Abstracted from a Ph.D. thesis at Rensselaer Polytechnic Institute.
- Harley, J. H. 1980. Sampling and measurement of airborne daughter products of radon. Reprinted as a landmark paper with comments by J. N. Stannard in *Health Phys.* 38:1067-74.
- Harley, N. H. and B. S. Pasternack. 1981. A model for predicting lung cancer risks induced by environmental levels of radon daughters. *Health Phys.* 40:307-16.
- Härtung, F. H. and W. Hesse. 1879. Der Lungenkrebs, die Bergkrankheit in den Schneeberger Gruben. *Vrtljhrsch f. gerichtl. Med.* 30:296, 31:102 and 313. [Cited from Hueper 1942.]
- Hewlett, R. G. and O. E. Anderson, Jr. 1962. *A history of the United States Atomic Energy Commission, vol. 1, The new world (1939-46)*. WASH-1214. Washington, D.C.: U.S. Atomic Energy Commission.
- Holaday, D. A. 1974. *Evaluation and control of radon daughter hazards in uranium mines*. Technical Information Report #75-117. Washington, D.C.: National Institute for Occupational Safety and Health.
- Holaday, D. A. 1979. Taped interview, July 9, 1979.
- Holaday, D. A. and H. N. Doyle. 1964. Environmental studies in the uranium mines. In *Radiological health and safety in mining and milling of nuclear materials*, vol. 1, pp. 9-20. Proceedings of a symposium held in Vienna, August 26-31, 1963. Vienna: International Atomic Energy Agency.
- Holaday, D. A., D. E. Rushing, R. D. Coleman, P. F. Woolrich, H. L. Kusnetz, and W. F. Bale. 1957. *Control of radon and daughters in uranium mines and calculations on biologic effects*, publ. no. 494. Prepared under the direction of W. M. Gafafer (technical adviser.) Washington, D.C.: U.S. Dept. of Health, Education, and Welfare, Public Health Service.
- Hollcroft, J. W. and E. Lorenz. 1951. The 30-day LD-50 of two radiations of different ion density. *J. Nat. Cancer Inst.* 12:533-44.
- Hollcroft, J. W., E. Lorenz, M. Matthews, and C. C. Congdon. 1955. Long-term survival following x irradiation and the irradiation of the α particles from radon and its decay products. *J. Nat. Cancer Inst.* 15:1059-69.
- Holmgren, R. M. 1974. Working levels of radon daughters in air determined from measurements of RaB + RaC. *Health Phys.* 27:141-45.
- Holtzman, R. B. 1970. Sources of ^{210}Pb in uranium miners. *Health Phys.* 18:105-12. [See also ANL-2489, pp. 37-43.]
- Horáček, J. 1969. Der Joachimstaler Lungenkrebs nach dem zweiten Weltkrieg (Bericht über 55 Fälle). *Z. Krebsforsch.* 72:52-56.

- Hueper, W. C. 1942. Cancers of the respiratory system. In *Occupational tumors and allied diseases*, ed. W. C. Hueper. Springfield, Ill.: C. C. Thomas.
- Hueper, W. C. 1955. *A quest into the environmental causes of cancer of the lung*. Public Health Service Monograph no. 36. Washington, D.C.: U.S. Department of Health, Education and Welfare.
- Hultqvist, B. 1956. Studies on naturally occurring ionizing radiations. K. Sven. Vetenskapssakad. Handl. ser. 4, band 6, no. 3; Stockholm, Sweden.
- Hursh, J. B. 1978. Personal interview at Rochester, N.Y.; May 31, 1978.
- Hursh, J. B., D. A. Morken, T. P. Davis, and A. Lovaas. 1965. The fate of radon ingested by man. *Health Phys.* 11:465-76.
- ICRP. See International Commission on Radiological Protection.
- Inhalation Toxicology Research Institute. 1979. Diesel Technology Toxicology Program. In *Inhalation Toxicology Research Institute Annual report 1978-79*. LF-69, pp. 199-272. Albuquerque, N. Mex.: Lovelace Biomedical and Environmental Research Institute.
- International Commission on Radiological Protection. 1977. *Radiation protection in uranium and other mines*. ICRP publ. 24. New York: Pergamon Press.
- International Commission on Radiological Protection. 1980. *Biological effects of inhaled radionuclides*. ICRP publ. 31. Oxford: Pergamon Press.
- International Commission on Radiological Protection. 1981. *Limits for inhalation of radon daughters by workers*. ICRP publ. 32. Oxford: Pergamon Press.
- ITRI. See Inhalation Toxicology Research Institute.
- Jackson, M. L. 1940. *The biological effects of inhaled radon*. M.S. degree thesis. Cambridge, Mass.: Mass. Institute of Technology.
- Jacobi, W. 1964. The dose to the human respiratory tract by inhalation of short-lived ^{222}Rn - and ^{220}Rn -decay products. *Health Phys.* 10:1163-74.
- Jammet, H. and J. Pradel. 1956. The problem of radon in uranium mines. In *Proceedings of the international conference on the peaceful uses of atomic energy*, vol. 13, pp. 219-21. Held in Geneva, August 8-20, 1955. New York: United Nations.
- Jansen, H. and P. Schultzer. 1926. Experimental investigations into internal radium emanation-Therapy I. Emanatorium experiments with rats. *Acta Radiol.* 6:631-46.
- JCAE. See Joint Committee on Atomic Energy.
- Joint Committee on Atomic Energy. 1967. *Radiation exposures of uranium miners*, pts. 1 and 2. Hearings before the 90th Cong. Washington, D.C.: U.S. Government Printing Office.
- Joint Committee on Atomic Energy. 1969. *Radiation standards for uranium mining*. Hearings before the 91st Cong. Washington, D.C.: U.S. Government Printing Office.
- Kunz, E., J. Ševc, and V. Plaček. 1978. Lung cancer mortality in uranium miners (methodological aspects). *Health Phys.* 35:579-80.
- Kunz, E., J. Ševc, V. Plaček, and J. Horáček. 1979. Lung cancer in man in relation to different time distribution of radiation exposure. *Health Phys.* 36:699-706.
- Kusák, V. 1969. Ethio-pathogenesis of bronchogenic pulmonary carcinoma in miners from uranium mines. *Strahlentherapie* 138:549-55.
- Kushneva, V. S. 1962. The radiotoxic action of radon. In *The toxicology of radioactive substances. I. Strontium, caesium, ruthenium, radon*, eds. A. A. Letavet and E. B. Kurlyandskaya, pp. 145-62. Oxford: Pergamon Press.
- Landahl, H. D. 1950. On the removal of air-borne droplets by the human respiratory tract: I. The lung. *Bull. Math. Biophys.* 12:43-56.
- Lewis, W. V. 1955. *Arthritis and radioactivity*. Boston, Mass.: Christopher Publishing House.
- London, Ye. S. 1904. Über die physiologischen wirkungen der emanation des radiums. *Zentrbl. f. Physiol.* 18:185-88. [Cited by Kushneva 1962.]
- Lorenz, E. 1944. Radioactivity and lung cancer; a critical review of lung cancer in the miners of Schneeberg and Joachimsthal. *J. Nat. Cancer Inst.* 5:1-15.
- Löwy, J. 1929. Über die Joachimstahler Bergkrankheit. *Med. Klinik* 25:141-42.
- Luckey, T. D. 1980. *Hormesis with ionizing radiation*. Boca Raton, Fla.: CRC Press.

- Ludewig, P. and E. Lorensen. 1924. Untersuchung der Grubenluft in den Schneeberger Gruben auf den Gehalt an Radiumemanation. *Z. Physik* 22:178-85; *Strahlentherapie* 17:428-35.
- Lundin, F. E., J. K. Wagoner, and V. E. Archer. 1971. Radon daughter exposure and respiratory cancer: Quantitative and temporal aspects. Joint Monograph no. 1 NIOSH and NIEHS, U.S. Department of Health, Education, and Welfare, Public Health Service.
- Maeda, K., S. Abe, Y. Kurokawa, and Y. Minagawa. 1974. Trial evaluation of the long-term survey of death causes in the population living near radiation rich hot spring. In *Proceedings of the 3d international conference of the International Radiation Protection Association*, ed. W. S. Snyder, CONF-730907-P1, pp. 491-94. Held in Washington, D.C., September 9-14, 1973. Oak Ridge, Tenn.: Technical Information Center.
- Mercer, T. T. 1975. Unattached radon decay products in mine air. *Health Phys.* 28:158-61.
- Mercer, T. T. and W. A. Stowe. 1971. Radioactive aerosols produced by radon in room air. In *Inhaled particles III*, ed. W. H. Walton, vol. 2, pp. 839-51. Proceedings of a symposium held in London, September 14-23, 1970. Old Woking, Surrey, England: Unwin Bros., Ltd.
- Mitchell, J. S. 1945. *Memorandum on some aspects of the biological actions of radiation with reference to tolerance problems*. H1-17. Montreal Laboratory.
- Morgan, K. Z. 1951. *Maximum permissible concentration of radon in the air*. Unpublished memorandum, April 10, 1951.
- Morgan, K. Z. 1954. *Maximum permissible concentration of radon in the air*. Unpublished memorandum, October 27, 1954.
- Morken, D. A. 1955a. Acute toxicity of radon. *AMA Arch. Ind. Health* 12:435-38.
- Morken, D. A. 1955b. *A radon exposure unit for small animals*. UR-307. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Morken, D. A. 1955c. *A survey of the literature on the biological effects of radon and a determination of its acute toxicity*. UR-379. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Morken, D. A. 1961. *The effect of inhaled radon on the survival, body weight, and hemogram of the mouse following single exposures*. UR-593. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Morken, D. A. 1964. *The effect of inhaled radon on the survival, body weight and hemogram of the mouse following multiple exposures*. UR-624. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Morken, D. A. 1969. The relation of lung dose rate to working level. *Health Phys.* 16:796-98.
- Morken, D. A. 1973a. The biological effects of radioactive noble gases. In *Noble gases*, eds. R. E. Stanley and A. A. Moghissi, CONF-730915, pp. 469-71. Washington, D.C.: U.S. Environmental Protection Agency.
- Morken, D. A. 1973b. The biological effects of radon on the lung. In *Noble gases*, eds. R. E. Stanley and A. A. Moghissi, CONF-730915, pp. 501-06. Washington, D.C.: U.S. Environmental Protection Agency.
- Morken, D. A. and J. K. Scott. 1966. *The effects on mice of continual exposure to radon and its decay products on dust*. UR-669. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Myers, D. K. and C. G. Stewart. 1979. *Some health aspects of Canadian uranium mining*. AECL-5970. Atomic Energy of Canada, Ltd.
- NAS-NRC. See National Academy of Sciences-National Research Council.
- National Academy of Sciences-National Research Council. 1968. *Radiation exposure of uranium miners*. Report of an advisory committee of the National Academy of Engineering to the Federal Radiation Council. Published by FRC, August 1968.
- National Academy of Sciences-National Research Council. 1971. *Epidemiologic studies of uranium miners*. Report to the Interagency Uranium Mining Radiation Review Group (IUMRRG), dated January 27, 1971.

- National Academy of Sciences-National Research Council. 1981. *Indoor pollutants*. Report prepared by the Committee on Indoor Pollutants of the Board of Toxicology and Environmental Health Hazards. Washington, D.C.: National Academy Press.
- National Bureau of Standards. 1941. *Safe handling of radioactive luminous compound*. NBS Handbook H-27, p. 3, May 2, 1941. Washington, D.C.: U.S. Government Printing Office.
- National Council on Radiation Protection and Measurements. 1975. *Natural background radiation in the United States*. NCRP report no. 45, Washington, D.C.
- National Council on Radiation Protection and Measurements. 1984a. *Evaluation of occupational and environmental exposures to radon and radon daughters in the United States*. NCRP report no. 78. Bethesda, Md.
- National Council on Radiation Protection and Measurements. 1984b. *Exposures from the uranium series with emphasis on radon and its daughters*. NCRP report no. 77. Bethesda, Md.
- NBS. See National Bureau of Standards.
- NCRP. See National Council on Radiation Protection and Measurements.
- Nero, A. V. and W. M. Lowder, eds. 1983. Indoor radon. *Health Phys.* 45(2):273-571.
- Parker, H. M. 1966. *Dosimetry related to uranium mining health hazards*. Research report prepared for the Federal Radiation Council. Richland, Wash.: Pacific Northwest Laboratory.
- Parker, H. M. 1969. The dilemma of lung dosimetry. *Health Phys.* 16:553-61.
- Pasternack, B. S. and N. Harley. 1971. Alpha dose to the human lung from radon daughters, thoron daughters and Pu-239. In *Research in environmental health sciences*, 8th annual report ES00260, pp. 183-85. New York: New York Univ. Medical Center.
- Pirchan, A. and H. Šikl. 1932. Cancer of the lung in the miners of Jáchymov (Joachimstal). Report of cases observed in 1929-1930. *Am. J. Cancer* 16:681-722.
- Pohl, E. 1962. Die Strahlenbelastung bei der Inhalation von Radium-Emanation. *Strahlentherapie* 119:77-96.
- Pohl-Rüling, J. and P. Fischer. 1982. An epidemiological study of chromosome aberrations in a radon spa. In Clemente et al. 1982, pp. 210-19.
- Pohl-Rüling, J. and F. Scheminzy. 1954. Das Konzentrationsverhältnis Blut/Luft bei der Radon-Inhalation und die Radon-Aufnahme in den menschlichen Körper im radioaktiven Thermalstollen von Badgastein/Böckstein. *Strahlentherapie* 95:267-82.
- Rajewsky, B. 1939. Bericht über die Schneeberger Untersuchungen. *Z. Krebsforsch* 49:315-40.
- Read, J. and J. C. Mottram. 1939. The "tolerance concentration" of radon in the atmosphere. *Br. J. Radiol.* 12:54-60.
- Reich, C. J. 1986. Therapeutic aspects of radon. [Draft manuscript sent to the author as a personal communication. Further personal communication, Calgary, Alberta, in April and November 1986.]
- Rostoski, Saupé, and Schmorl. 1926. Die Bergkrankheit der Erzbergleute in Schneeberg in Sachsen ("Schneeberger Lungenkrebs"). *Z. Krebsforsch* 23:360-84.
- Saccomanno, G. 1981. Cancer of the lung in uranium miners. In Gomez 1981, pp. 203-04.
- Saccomanno, G., V. E. Archer, O. Auerbach, M. Kuschner, M. Egger, S. Wood, and R. Mick. 1981. Age factor in histological type of lung cancer among uranium miners, a preliminary report. In Gomez 1981, pp. 675-79.
- Schultzer, P. 1926. Experimental investigations into internal radium emanation Therapy II. On the cause of the effect on rats of continuous emanatorium treatment. *Acta Radiol.* 6:647-57.
- Scott, J. K. 1955. *The histopathology of mice exposed to radon*. UR-411. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Ševc, J., E. Kunz, and V. Plaček. 1976. Lung cancer in uranium miners and long-term exposure to radon daughter products. *Health Phys.* 30:433-37.

- Seven-State Conference. 1955. *Seven-state uranium mining conference on health hazards*. Proceedings of a conference held in Salt Lake City, February 22-23, 1955 with official representatives from Arizona, Colorado, Idaho, New Mexico, South Dakota, Wyoming, and Utah.
- Seymore, F. W., R. M. Ryan, and J. C. Corelli. 1980. Radon and radon daughter levels in Howe Caverns. *Health Phys.* 38:858-59.
- Shapiro, J. 1954. *Evaluation of the pulmonary radiation dosage from radon and its daughter products*. UR-298, Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Shapiro, J. 1956. Radiation dosage from breathing radon and its daughter products. *AMA Arch. Ind. Health* 14:169-77.
- Shapiro, J. V. and W. F. Bale. 1953. *A partial evaluation of the hazard from radon and its degradation products*. UR-242, pp. 6-18. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Šikl, H. 1930. Über den Lungenkrebs der Bergleute in Joachimstal (Tschechoslowakei). *Z. Krebsforsch* 32:609-13.
- Smyth, H. D. 1948. *Atomic energy for military purposes: The official report on the development of the atomic bomb*. Under the auspices of the U.S. Government, 1940-1945. Princeton, N.J.: Princeton Univ. Press.
- Stannard, J. N. 1958. An evaluation of inhalation hazards in the nuclear energy industry. In *Proceedings of the 2d United Nations international conference on the peaceful uses of atomic energy*, vol. 23, pp. 306-12. Held in Geneva, September 1-13, 1958. Geneva: United Nations.
- Stannard, J. N. 1973. Toxicology of radionuclides. *Annu. Rev. Pharmacol.* 13:325-57.
- Stannard, J. N. 1980. Breathing is an old habit. In *Pulmonary toxicology of respirable particles*, eds. C. L. Sanders, F. T. Cross, G. E. Dagle, and J. A. Mahaffey, CONF-791002, pp. 616-24. Proceedings of the 19th annual Hanford life sciences symposium held in Richland, Wash., October 22-24, 1979. Springfield, Va.: National Technical Information Service.
- Steinhäusler, F., E. Pohl, and W. Hofmann. 1982. On the suitability of epidemiological studies of population groups exposed to elevated levels of radon and daughters. In Clemente et al. 1982, pp. 259-67.
- Stewart, C. G. 1971. *Chronology of uranium mining health protection activities*. Revised January 4, 1971. Unpublished, received as personal communication.
- Stewart, C. G. and S. D. Simpson. 1964. The hazards of inhaling radon-222 and its short-lived daughters: Consideration of proposed maximum permissible concentrations in air. In *Radiological health and safety in mining and milling of nuclear materials*, vol. 1, pp. 333-57. Proceedings of a symposium held in Vienna, August 26-31, 1963. Vienna: International Atomic Energy Agency.
- Sultzter, M. and J. B. Hursh. 1954. Polonium in urine of miners exposed to radon. *Arch. Ind. Hyg. and Occup. Med.* 9:89-100.
- Suomela, M. and H. Kahlos. 1972. Studies on the elimination rate and the radiation exposure following ingestion of ^{222}Rn rich water. *Health Phys.* 23:641-52.
- Tschelnitz, H. 1935. Physikalische Bemerkungen zum Ätiologie des St. Joachimsthaler Lungenkarzinoms. *Strahlentherapie* 53:269-75.
- Tsivoglou, E. C. 1956. Use of radioisotopes in studies of health hazards in the uranium mining industry. In *Proceedings of an international conference on the peaceful uses of atomic energy*, vol. 13, pp. 237-41. Held in Geneva, August 8-20, 1955. New York: United Nations.
- Uhlig, M. 1921. Über den Schneeberger Lungenkrebs. *Virchows Arch. Pathol. Anat. Physiol.* 230:76-98.
- Union Carbide Corporation. 1952 et seq. *Mesa miracle*. [Revised and updated in 1955, 1956, 1961, and 1963.] New York: Union Carbide Corporation.
- United Nations Scientific Committee on the Effects of Atomic Radiation. 1977. *Sources and effects of ionizing radiation*. 1977 Report to the General Assembly. New York: United Nations.

- United Nations Scientific Committee on the Effects of Atomic Radiation. 1982. *Ionizing radiation: Sources and biological effects*. 1982 Report to the General Assembly; with annexes. New York: United Nations.
- UNSCEAR. See United Nations Scientific Committee on the Effects of Atomic Radiation.
- U.S. Congress. 1979. *Health effects of low-level radiation*. Hearings before the Senate Subcommittee on Health and Scientific Research. June 19, 1979.
- Wagoner, J. K., V. E. Archer, B. E. Carroll, D. A. Holaday, and P. A. Lawrence. 1964. Mortality patterns among United States uranium miners and millers, 1950 through 1962: Preliminary report. In *Radiological health and safety in mining and milling of nuclear materials*, vol. 1, pp. 37-48. Proceedings of a symposium held in Vienna, August 26-31, 1963. Vienna: International Atomic Energy Agency.
- Weibel, E. W. 1963. *Morphometry of the human lung*. New York: Academic Press.
- Whittemore, A. A. and A. McMillan. 1983. Lung cancer mortality among U.S. uranium miners: A reappraisal. *J. Nat. Cancer Inst.* 71:489-99.

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Capsule Chronology

Polonium

- 1898** Discovery of polonium, the first radioactive element to be separated from its ores (M. Curie).
- 1924-1938** Animal work by Lacassagne in France.
- 1930s** Chemistry worked out.

WORLD WAR II

Metallurgical Laboratory (Chicago) studies of distribution and excretion, later toxicity relative to radium.

University of Rochester studies of behavior of ^{210}Po after injection, inhalation, ingestion, skin absorption, etc.; biological effects and toxicity relative to plutonium and radium. Includes injection of a few hospital patients.

Manufacture of large quantities of polonium at "Dayton Project." Use in initiator for early nuclear devices. Biomedical research begins when the Dayton Project becomes "Mound Laboratory" at the end of the war.

POST-WORLD WAR II

- 1947-1964** Continuation and expansion of basic biochemistry, solution chemistry, physiology, and pathology at University of Rochester. Many varieties of cancer induced.
- 1948-1960s** Active biomedical program at Mound Laboratory (Dayton, Ohio).
- 1950s** Expansion of MED work on polonium at Chicago (M. Finkel, Argonne National Laboratory). Mostly relative toxicity, acute toxicology, and long-term effects.
- 1951** Effect of BAL on excretion and tissue distribution of polonium (Hursh at Rochester).
- 1956** Moyer monograph on polonium published (AEC Monograph, TID-5221).
- 1950s-1970s** USSR work on polonium published and translated at intervals. Summarized in 1971 and 1972.
- 1960s** Polonium studied in the arctic food chain (see also chapter 15).
- Mid-1960s** Interest develops in polonium in cigarette smoke as possible causative agent of lung cancer in smokers.
- 1964** Rochester work summarized as supplement to *Radiation Research*. Includes functional changes (Stannard, Casarett, and colleagues).
- 1964 et seq.** Interest in polonium excretion as a measure of radon exposure in uranium miners.
- 1972-1974** Polonium studied in marine algae (Folsom, Hodge, et al., Scripps Institution of Oceanography).
- 1973** Metabolic ward studies (Holtzman, Argonne National Laboratory).
- 1974 et seq.** Harvard studies of polonium in lung (Little and Kennedy).
Lung cancer produced in hamster.

Thorium

- 1899** Radioactive gaseous emanation from thorium described (Rutherford).
- 1900** Thorium-234 discovered (Crookes).
- 1905** Thorium-228 discovered (Hahn).
- 1907** Ionium (thorium-230) discovered (Boltwood).
- 1900 on** Use in gas mantles as thoria. Later as radiopaque medium.
- 1912-1940** Work in many countries on effects of thorium on a variety of organisms from unicellular to mammalian. Largely looking for chemical toxicity-as a rare earth, but some work with isotopes of higher specific activity. Production of sarcomata in animals shown with colloidal thorium dioxide (Thorotrast) in the 1930s.

WORLD WAR II

Mostly a silent period in biomedical work except concern for Thorotrast patients and thorium workers in gas mantle and metallurgical factories. Use as a nuclear fuel considered, and a small amount of work carried out on its toxicity, largely chemical, at Rochester.

POST-WORLD WAR II

- 1946, 1947** Tracer work at Berkeley published (Hamilton and Lanz). Done under Metallurgical Laboratory auspices during war.
- 1950 et seq.** Biomedical work with thorium at Western Reserve University.
- 1952** Importance of carriers and concentration demonstrated (Scott at Rochester).
- 1957** Thorotrast metabolism studied in man (Hursh at Rochester and Looney at Bethesda).
- 1958** Boone studies at Los Alamos (ionium).
- 1958-1969** Unraveling of metabolism of the seven thorium isotopes in man (Argonne National Laboratory and MIT).
- 1959-1960** Chemical toxicity of "natural thorium" (Downs, Hodge, and Thomas at Rochester). Rochester conference.
- 1959** Special curie for thorium proposed.
- 1960s** Thorium isotopes enter the Utah beagle experiment.
Reports throughout the 1960s and 1970s. Complex dosimetry worked out.
- 1960s** USSR work reported in a book by Letavet and Kurlyandskaya and reviewed by Moskalev.
- 1961** Thomas studies at Rochester.
- 1960s-1980s** Thorotrast work continues in laboratories and clinics in many countries.
- 1963** Inhalation experiment at Rochester (Boecker).
- 1966** Survey of thorium workers (Albert).
- 1968-1979** Several symposia on Thorotrast.
- 1971** Thorium-228 tops the list in producing osteosarcoma in the Utah beagles.

1974 Special curie for uranium and thorium abandoned. Suggested that "natural thorium" does not have a constant composition, and the term should be discarded (Hursh, NCRP).

1975 et seq. Effort concentrated on Thorotrast cases and animal experiments to delineate role of chemical toxicity in effects seen.

Thorium work with beagles at Utah completed.

Thorium epidemiology of factory workers begins.

Chapter 4

Polonium and Thorium

Overview

This chapter describes, separately, some of the more cogent biomedical research activities and health effects noted with the last two of the important naturally occurring radionuclides: polonium and thorium (see preface to this chapter).

As we saw in chapter 3, two of the most significant radionuclides in the radon decay chain, from the standpoint of health effects, are isotopes of polonium. Therefore, in a sense it can be said that the radon daughter problem is to a significant degree a polonium problem. However, the isotopes of most importance in the radon decay chain are of such short half-life that they cannot be studied in isolation from the other daughter products. Therefore, the biomedical research with polonium has used primarily ^{210}Po . This isotope has a 138-day half-life. Although it is a member of the radon decay chain, it is blocked from significant effect in reasonable time by the 21-year-half-life, ^{210}Pb , which precedes it. Polonium-210 was the predominant isotope isolated from radium by Madame Curie. It has been prepared more recently by neutron bombardment of bismuth.

Polonium differs greatly from most of the other alpha-particle-emitting radionuclides, both natural and artificial, in that it deposits mostly in soft tissue. It does not deposit in bone to any appreciable extent, although it may be produced in situ by the decay of ^{210}Pb already present in bone. Polonium has a strong affinity for the red blood cells and forms radiocolloids with ease. It is easily carried to tissues of the reticuloendothelial system (RES) with resultant high doses to spleen and liver. Much is also deposited in kidney as a result, in part, of its carriage in blood, and in part its fairly ready passage into the kidney tubules.

Since its degradation product is not radioactive (i.e., stable lead), and ^{210}Po is fairly readily obtained in high purity, biomedical research with it has provided an opportunity to study the effects of alpha radiation in comparative isolation from other radionuclides. The chapter reviews the early work with polonium by Lacassagne in France, the rather concentrated research devoted to it by the Manhattan Engineer District (MED) laboratories during World War II, the further work at these installations in the postwar period, and the recent notions that naturally occurring polonium in and on tobacco leaves may play a key role in the generation of lung cancer in cigarette smokers.

Biomedical research with thorium in its various forms is far more complex than that with polonium. Not only is the thorium series itself complex, but thorium isotopes of significance occur in other series (see preface to these four chapters). It deposits readily in bone, but it also forms exceedingly insoluble complexes in other tissues. Also, because of its low specific activity, there is opportunity for chemical toxicity in addition to radiation effects, although this is a relatively minor consideration compared to natural uranium. There is a significant worker population that has used thorium in various forms. The epidemiology of these populations is just beginning to be addressed and is described briefly in this chapter.

Probably the most significant exposures of humans to thorium isotopes have come from a radiopaque medium called "Thorotrast." This colloidal preparation deposited essentially permanently in the liver and other RES elements. While the involved thorium isotopes are basically only weakly radioactive, the long periods of exposure led to significant doses to many patients. Liver tumors have appeared in the several populations involved. These populations, both in the United States and abroad, are considered in the chapter along with the factory populations and the fairly extensive amounts of animal research. Considerations of thorium in the environment are put off to the sequence in chapters 11-15.

Prologue

Before launching into the discussion of polonium and thorium, it should be noted that, while these are the last two of the naturally occurring radionuclides we will consider in any detail, there are others. These are frequently referred to as "nonseries" radionuclides. Most of them have little toxicologic significance in the amounts normally seen in nature. Only through the activities of man, e.g., the production of ^{14}C and ^3H in nuclear reactions, do concentrations of these reach potentially significant levels. We will hold their review for later chapters. These "nonseries" radioisotopes are discussed briefly in the preface to these four chapters on naturally occurring radionuclides and are listed there in table PN-1.

The two elements considered here, polonium and thorium, occur as steps in some of the series as outlined in the preface.

Polonium presents a relatively straightforward problem compared to many we have considered thus far. By contrast, thorium isotopes present very complex problems and many dilemmas that research to date has only partially solved.

Part A. Polonium

I. Introduction

Polonium (element 84) was the first radioactive element Madame Curie separated from pitchblende. As is well known, she named it after her home country, Poland. It has twenty-five isotopes from mass number 192 to 218, all of them radioactive. As will be seen from table 4.1, most of the isotopes have very short half-lives. Only 208, 209, and 210 have half-lives sufficiently long to be of interest for experimental toxicologic research, although 214 and 218 are of significance in the radon daughter problem, as we saw in chapter 3. Of these isotopes, ^{210}Po is by far the most commonly encountered and is the one worked with

TABLE 4.1. Polonium Isotopes and Their Nuclear Properties

Isotope Mass	Mode of Decay		Alpha Energy (Mev)	Method of Production*
	Half-Life	Emissions		
192	0.5 s	α	6.58	Bi + p
193	4 s	α	6.47	Bi + p
194	13 s	α	6.38	Bi + p
195	30 s	α	6.26	Bi + p
196	1.9 m	α	6.14	W + Ne
197	~4 m	α	6.040	Bi + p; $P_t + C^{26}$
198	~6 m	α	5.935	Bi + p
199	~11 m	α	5.846	Bi + p
200	~8 m	e, α	5.770	Bi + p
201	18 m	e, α	5.671	Bi + p
202	43 m	e, α	5.575	Bi + p
203	45 m	e	5.48	Bi + p
204	3.8 h	e, α	5.370	Bi + p
205	1.8 h	e, α	5.22	Pb ²⁰⁴ + α
206	8.8 h	e, α	5.21	Pb ²⁰⁴ + α
207	5.7 h	e, α	5.10	Pb ²⁰⁶ + α
208	2.93 y	α	5.08	Pb ^{206,207} + α
209	103 y	α ,e	4.877	Bi + p; Bi + d
210 (RaF)	138.4 d	α	5.3054	Bi + p; Bi + d natural; pb + α ; Bi + d; Bi + p; Bi + n
211 (AcC')	0.52 s	α	7.43	natural
211	25 s	α	7.14	Pb ²⁰⁸ + α
212 (ThC')	3×10^{-7} s	α	8.776	natural
213	4.2×10^{-6} s	α	8.35	Rn ²¹¹ α Bi ²¹³ β
214 (RaC')	1.637×10^{-4} s	α	7.68	natural
215 (AcA)	1.83×10^{-3} s	α , β	7.365	natural
216 (ThA)	0.158 s	α	6.774	natural
217	<10 s	α	6.5	Rn ²²¹ α
218 (RaA)	3.05 m	α , β	5.998	natural

*e: electron capture; p: proton; d: deuteron.

Source: Modified and reset from Haissinsky 1961.

biomedically. With an almost pure alpha emission and a half-life neither too long nor too short, chemical properties resembling the rare earths and quite different from those of radium and plutonium, ²¹⁰Po has been much used as a source of alpha particles for many purposes. Furthermore, it is the last radioactive member, and a significant one, of the radium series as it occurs in nature.

In this chapter, we will be referring so regularly to the 210 isotope that we will not give numbers unless other isotopes of polonium are involved. The 210 isotope decays with a 138-day half-life to a stable lead isotope (^{206}Pb), and the decay has virtually no contamination with beta or gamma radiation. (One decay in 10^5 is a gamma of low energy, 0.8 MeV, and there are still lower-energy x rays.) In the earlier days of describing the radium decay series, ^{210}Po was called "Radium-F" and ^{206}Pb was called "Radium-G."

Polonium has been used extensively as an alpha-particle source in the production of neutrons by its reaction, for example, with beryllium. Many large sources were prepared before plutonium became available in sufficient quantities to supplant it. In fact, it was the alpha source in the neutron-producing initiator for at least the first generation of atomic weapons and was produced in large quantities during the MED days. Because of the relatively short half-life, production had to continue even though the weapons were not used. A project known as the Dayton Project, operated by the Monsanto Chemical Company in and around Dayton, Ohio, was engaged in the production of ^{210}Po for neutron sources.

Polonium has also found wide application in static eliminators for many commercial processes, such as paper plants where the accumulation of static electricity on moving machinery can lead to disastrously erratic behavior of the material passing through. But it has proven difficult to contain the polonium on the eliminator bars, and several cases of considerable contamination have been reported. (See for example Robertson and Randle 1974.)

Other instances of contamination have resulted from breaking of alpha or neutron sources containing polonium. (See for example Callihan and Ross 1952; Scott and West 1975.) Also, polonium has a very marked tendency to "creep" if left in the open in either solution or solid form. A laboratory that was clean on Friday evening may be found widely contaminated with polonium alphas on Monday morning from a source left in the open on a laboratory bench, or even in a hood.

Despite these instances and others, direct contamination of man with ^{210}Po is a rare bird in comparison with radium, uranium, and the radon daughters in uranium mines^(a) reviewed in the previous chapters. Primary reasons for interest in it lie in its research uses and potential for contamination and the consequent need for information upon which to base permissible exposures.

II. Early Research

Polonium has long been a very useful tool in physics and physical chemical research because of its energetic and almost pure alpha-particle emissions. For the same reason, it was a good candidate for use in biomedical research. But only one major effort took place in the years before World War II. This was work by Lacassagne and colleagues in France, results of which were published over the years 1924 to 1938. The papers were mostly in the *Comptes Rendues* and *Journal de Radiologie et de l'Electrologie*, and were nicely summarized by

(a) It should be noted, however, that the principal radiation dose from radon daughters is contributed by two polonium isotopes, ^{218}Po with a 3-min half-life and ^{214}Po with a half-life of 104 sec. Thus, the radon daughter problem is partly a polonium problem, and this adds impetus to knowing its biomedical behavior (chapter 3).

Silberstein in a volume of the National Nuclear Energy Series (NNEs) (Silberstein 1950). A smaller effort was reported by Fernau and colleagues (1913).

Lacassagne used rabbits primarily and injected the polonium in dilute HCl. His work made it apparent that polonium was biochemically and pharmacologically very different from radium. This was no surprise, for its chemical characterization (e.g., Haissinsky 1961) had already indicated that it was different. The principal differences are its more generalized distribution among tissues in contrast to the tendency of radium to localize in bone; its easy hydrolysis to form insoluble colloids, which are taken up by organs of the reticuloendothelial system (RES); and its concentration in kidney cortex and interstitial tissue of the testes. Some pioneering autoradiographic work helped with these localizations.

Kidney and spleen had the highest concentrations at early times. Spleen rose to be over tenfold higher than the kidney at about sixty days, then fell back somewhat. Elimination was fairly rapid with a biological half-life of about forty days.

A serious problem with Lacassagne's work was the low recoveries from tissues and excreta. Combined, they did not exceed 12% of the dosage thought to have been administered. This led Lacassagne to postulate that large portions of the dose were excreted through lungs and skin, but no measurements of these were recorded. A more likely explanation, as Silberstein (1950) pointed out, is incomplete plating of the polonium on the silver foil used for measurement. The solutions contained fat and solids, which could easily have interfered with the plating. Another possibility is that the dose actually administered was much lower than thought to be, because of the distressing tendency of polonium (and many other radioelements) to deposit on glass surfaces. The technique of "dummy injection," so commonly used in radioisotope research from the 1940s on, is not mentioned in this early work.

Despite the technical problems of recovery, it is impressive to note how well the relative concentration of polonium in major organs tallies with later work.

Finally, it is clear that the statement that polonium is more or less uniformly distributed is true only in a relative sense. While there are not the striking contrasts seen with the bone seekers, there are manifold differences between the highest and the average tissue content.

III. Polonium Research During World War II

A. The Setting

The principal sites of biomedical research on polonium under the Manhattan District were the Metallurgical Laboratory at Chicago, where work started rather late in the war years, and the University of Rochester Project, which engaged in work on the comparative toxicology of three important alpha emitters (polonium, plutonium, and radium), plus some very necessary studies of the metabolism (i.e., distribution and excretion) of polonium and radium. The *raison d'être* was partly the establishment of relative toxicity ratios to help set exposure standards for plutonium (see chapters 6, 7, and 16). But there was a need also for much more information on ^{210}Po itself, for it was being prepared in considerable quantities at the Dayton Project. Therefore, the work, especially at Rochester, delved fairly deeply into the behavior of polonium in biological systems in its own right, as well as comparative toxicity studies.

It is doubtful if many of those engaged in the work knew the reasons for doing it. Security was tight. The very existence of the Dayton Project was not generally known, even though it managed to contaminate the former Runnymede Playhouse in a fine residential suburb of Dayton so badly that it had to be demolished in February 1950. Also, it transformed the old Bonebrake Theological Seminary, leased by Monsanto, so thoroughly that extensive renovation and decontamination were needed to return it to the Board of Education in 1950. In fact, at its peak, the Dayton Project was using twenty buildings around Dayton for research and the extraction and purification of polonium from materials of various origin, from radium residues from the Port Hope, Ontario radium refinery to irradiated bismuth from the Clinton Reactor (Moyer, Gnagey, and Rogers 1956). Records as to the number of workers are not easy to find, but there were clearly enough to make a full-blown biomedical investigation worthwhile for the setting of standards. Until the very end of the war, when the Dayton Laboratory began to develop a biomedical research group of its own, most of the needed data and advice for standard setting came from the Rochester Project, particularly from William F. Bale, Robert Fink, and, toward the end of the war, John B. Hursh.

The code name for polonium in the MED days was "Postum."^(a) Only a few in the very top echelons were supposed to know its translation. However, anyone with a good chemistry background should not have had much difficulty in translating a code name whose first two letters spelled out the chemical symbol for the element, especially if they also knew it was an alpha emitter with amphoteric properties. (The code name "Tuballoy" for uranium was probably a better choice for a cover.)

Nevertheless, postum or polonium, or just "solution-x," the Rochester and to a lesser extent the Chicago group took up where the Lacassagne work left off. This is the subject of the next section.

B. Distribution and Excretion

1. Methodology

The results of over five years of work at Rochester were made available in the usual internal reports, which were issued as often as monthly. For our purposes, we can rely primarily on the volume in the NNES series edited by Fink (Fink 1950) and the Argonne National Laboratory (ANL) reports after the war.

One of the first areas of attack was analytical technique. Polonium plates spontaneously on a number of metals, but also on nearly every other surface at hand. The Rochester group spent much effort on getting a good digestion procedure that would oxidize the troublesome interfering substances, particularly fat, and present a clear solution that could be set up for plating on silver foil with confidence. An entire chapter in the Fink volume is devoted to details of the general methods (Gorham et al. 1950).

Dry ignition was precluded because of the high volatility of polonium at elevated temperatures. The best recoveries were obtained with a mixture of 70% perchloric acid plus concentrated nitric acid. This had the disadvantage of extreme instability in the presence of fat. This produced some of the explosive oxides of chlorine, and there were accidents. But no better procedure appeared,

(a) The corresponding name for plutonium was "Product."

and the danger of explosion was kept as low as possible by always using relatively small aliquots and multiplying the number of digestions if necessary. (A whole rat carcass, for example, would be divided into several fractions, or special precautions would be taken in the heating process.)

By constant attention to detail, the recovery in the plating process was improved markedly, even approaching 100%. The set-up for plating is described with diagrams in the cited chapter. This basic system was adapted to the large numbers of samples needed in the routine biological monitoring at various sites.

Even with the best technique, it was not possible to prepare injection solutions by simple dilution and be sure of their polonium concentration. Therefore, the technique of the "dummy injection" was routinely applied. This amounted to repeating the "injection" immediately after the real injection, but emptying the contents of the syringe into a known volume of fairly strong acid. The measured content of this solution became the administered dose, no matter what the intended dose was. Fortunately, so long as the solution was kept strongly acid, the polonium did not precipitate or plate out. But as soon as the pH rose toward neutrality, the plating out and colloid formation began.

For the war work, the stock solution was neutralized just before injection with moderately strong alkali. As we will see in the postwar work, this almost inevitably produced at least some insoluble complexes. We can be sure that the injection solutions contained from some to considerable amounts of insoluble complexes and radiocolloids. This must be kept in mind as we review the distribution and excretion results.

A special glass metabolism cage was built in sizes suitable for rats or rabbits to separate urine from feces. Much work was done to perfect both their design and surface preparation. (Plastics were not yet available. Stainless steel, used so much in the Plutonium Project, was in short supply and might not have worked well anyway.)

2. Animal Studies

The animal studies on distribution and excretion of polonium involved, at Rochester, intravenous and subcutaneous injection, oral administration by gavage, and inhalation of volatilized polonium in the white rat, absorption through the skin of the mouse, and intravenous injection in the rabbit (Silberstein et al. 1950). At Chicago, the studies were by intravenous injection in CF1 mice (Finkel et al. 1949). The bulk of the work was done by intravenous injection at both laboratories, with other routes primarily used for a quick comparison.

At Rochester, detailed measurements were made of both urinary and fecal excretion with daily measurements out to as long as three hundred days. The animals (rats) received from 1.5 to 30 $\mu\text{Ci/kg}$ body weight. Fecal excretion exceeded urinary by factors up to ten at all times. The fecal excretion after intravenous administration was largely via the bile, as testified to by an experiment in which the bile duct was ligated.

Figure 4.1, taken from the Fink volume, illustrates the kinetics of loss. Retention was, of course, the inverse of this relation. The half-time was, on the average, about twenty-five to thirty days on the basis of percentage of dose, about forty-five days on the basis of microcuries lost per 100 μCi injected (see figure 2.7 in Fink 1950, p. 52). Obviously, polonium is lost more rapidly than many of the bone-seeking elements.

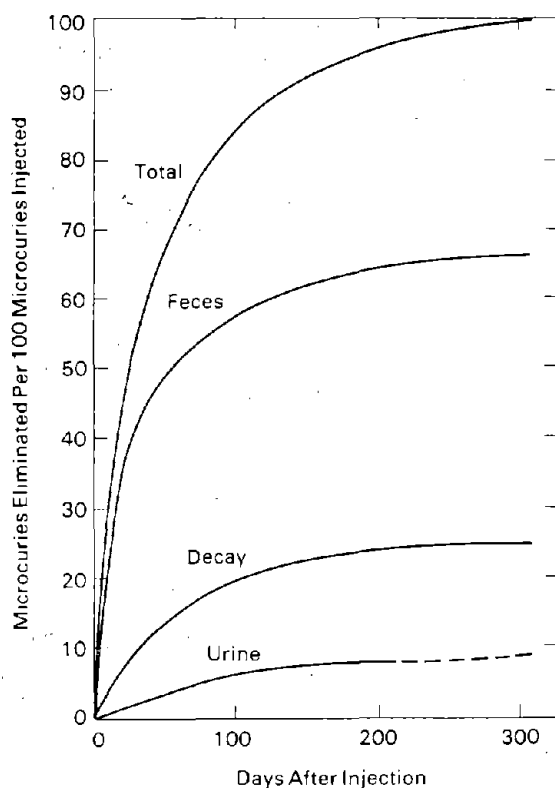


FIGURE 4.1. Excretion of polonium by the rat following intravenous injection. (Redrawn from Fink 1950, p. 51.)

The distribution among the tissues can be best described by reproducing two diagrams from the Fink volume. Figure 4.2 shows the percentage of dose per gram at four selected times after intravenous administration to the rat. Spleen, as an active organ of the RES, has the highest content at all times. Kidney, while lower, is surprisingly high for not being an RES organ.

In figure 4.3, the information is presented as percentage of body content per gram of tissue. This mode of expression gives a better view of shifts in tissue distribution with time since it combines the factors of decay and elimination that affect the perspective, at long times especially.

After intravenous administration, the two modes of expressing the data are remarkably similar. The primary exception is the climbing of red blood cells as a fraction of the body burden, a subject we shall return to when considering the postwar work.

The distribution after intravenous administration in the rabbit was somewhat different from what it was in the rat, with higher concentrations in kidney and testis, for example, but lower concentrations in spleen, pancreas, and thymus. The rabbit kidney concentration was four times higher than any other tissue. Perhaps because of this, urinary excretion was much higher in the rabbit than in the rat.

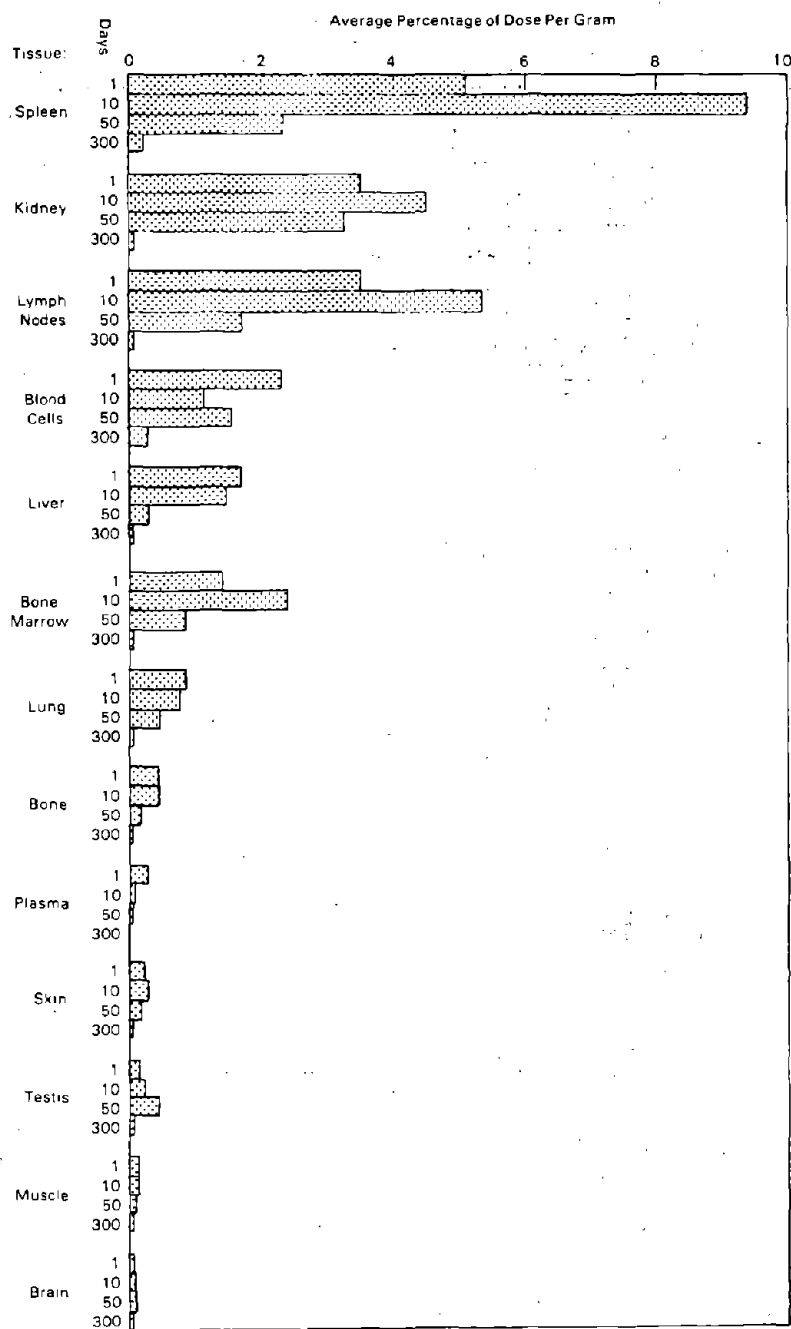


FIGURE 4.2. Percent dose per gram in rats after intravenous administration of polonium chloride. (Redrawn from Fink 1950, p. 54.)

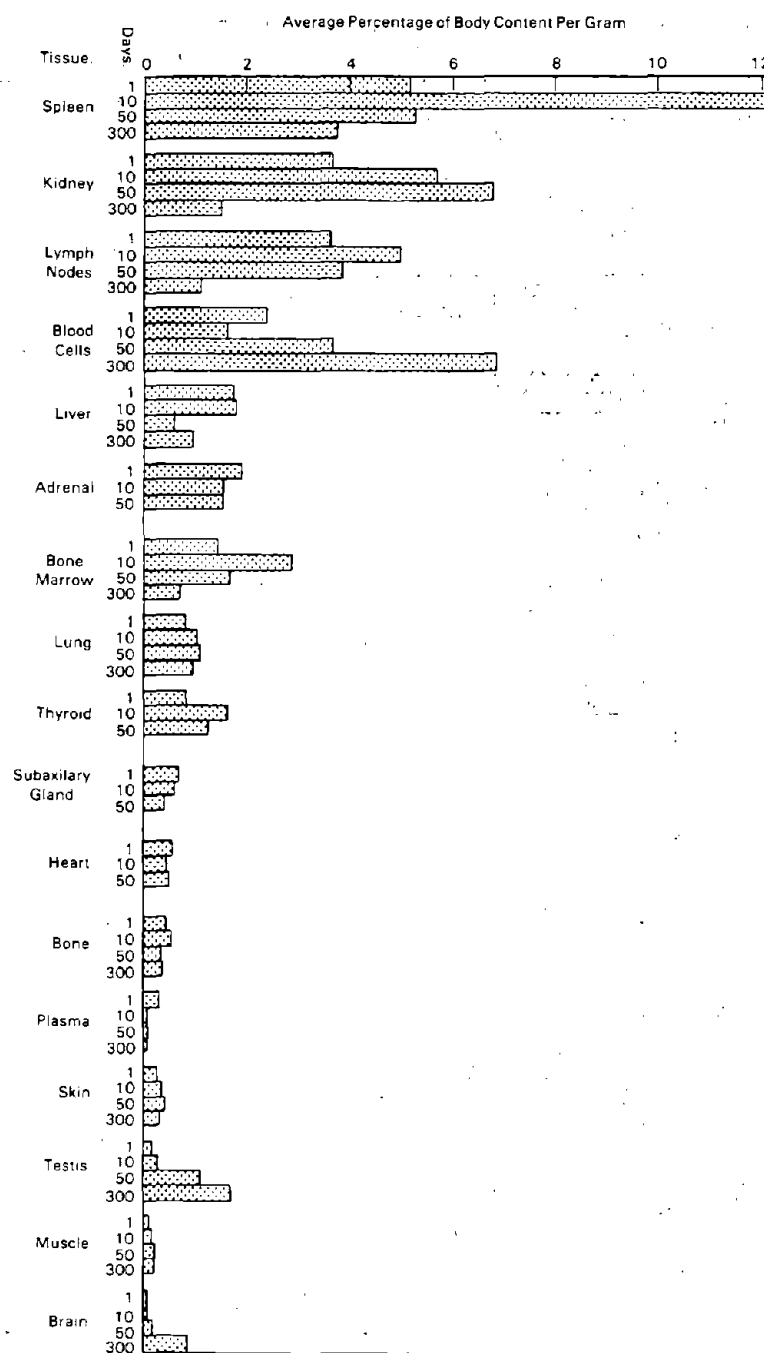


FIGURE 4.3. Percent body content per gram in rats after intravenous administration of polonium chloride. (Redrawn from Fink 1950, p. 60.)

After subcutaneous administration, there was a higher kidney content and higher urinary excretion for about one day. Otherwise, the distribution and excretion were quite similar to that after intravenous administration.

There were some surprises after oral administration. There was the usual high fecal excretion associated with a relatively poorly absorbed element (less than 10% absorption), and an increase in urinary excretion, which is always hard to interpret because of possible contamination of the urine from feces. But there were other significant differences. The concentrations in RES tissues were relatively lower than after intravenous administration, while the concentration in red cells was markedly high.^(a) Indeed, the red cells show the highest concentration found in any tissue, accounting for from one-fourth to one-half of the total amount in the body at ten days after gavage.

The authors speculate briefly that there must be an important difference in the chemical state of polonium entering the blood by absorption from gut compared to that introduced directly into the blood stream.

The inhalation studies involved fairly elaborate equipment for bringing air laden with polonium volatilized from a hot wire to animals. Volatilization is easy because of the low temperatures at which polonium volatilizes. The exposures were done either singly, with only the animal's snout in the air stream, or in groups of fifteen to twenty rats in 12-in.-diameter glass jars. Careful measurements were made not only of the initial deposition in lung, but of the transfer to other tissues. As expected, the lung had the highest concentration initially, and it fell rapidly in the first two days. Not fully expected was that some polonium appeared to settle in the lung for a more extended stay.

Autoradiographic studies showed rapid clearance of polonium from the bronchial walls with patches of dense activity further into the alveolar tissues. Thus, despite being a "relatively soluble" substance, the polonium was clearly aggregating either through physical-chemical processes or by the action of phagocytes.

The amounts after inhalation, as fraction of the body content, in other important tissues such as spleen, kidney, liver, lymph nodes, etc., were in the same range or a little lower than by other routes. There was a small indication of increased amounts in red cells.

Twelve experiments were done to observe the absorption and distribution of polonium placed on the skin of the mouse. The solvent was saline, and absorption was very low. Absorption from organic solvents was not tried.

The Chicago (Argonne National Laboratory) work with polonium began toward the end of the war. As we will see in chapters 7 and 8, it was part of a large-scale experiment on relative toxicity of alpha emitters. But there were special studies made of polonium in its own right.

A short summary of distribution and excretion in the CF1 mouse is given by Finkel et al. (1949) in an ANL report and by Finkel and colleagues in a published paper (Finkel et al. 1953). Total amounts in organs are shown in figure 4.4A and concentrations in figure 4.4B.

Spleen and kidney maintain the position seen in the Rochester experiments with the rat, but with spleen even higher. For example, at 120 days after intravenous injection, the whole spleen contained 97% of the polonium. The ovaries contained significant amounts on a concentration basis. This led the authors to

(a). This elevation persists over long periods, even beyond the life span of the red cell in the rat.

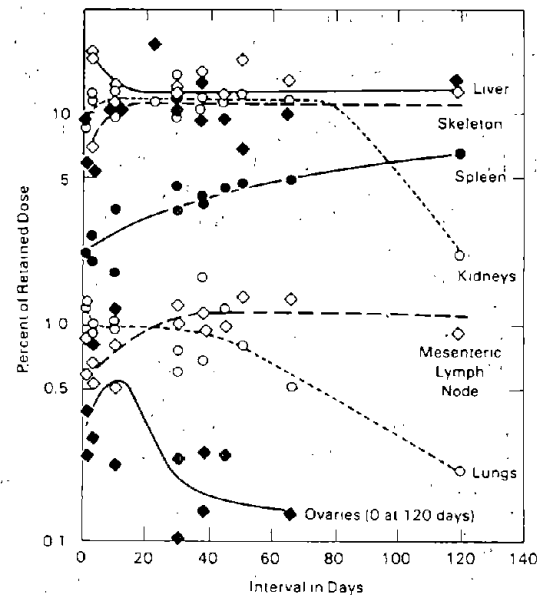


FIGURE 4.4A. Distribution of retained polonium in the CF1 mouse. The scale is μCi in organ $\times 100$ divided by μCi in total animal. (Redrawn from Finkel et al. 1953. Reprinted with permission of The Williams & Wilkins Co., Baltimore, Maryland, copyright 1953.)

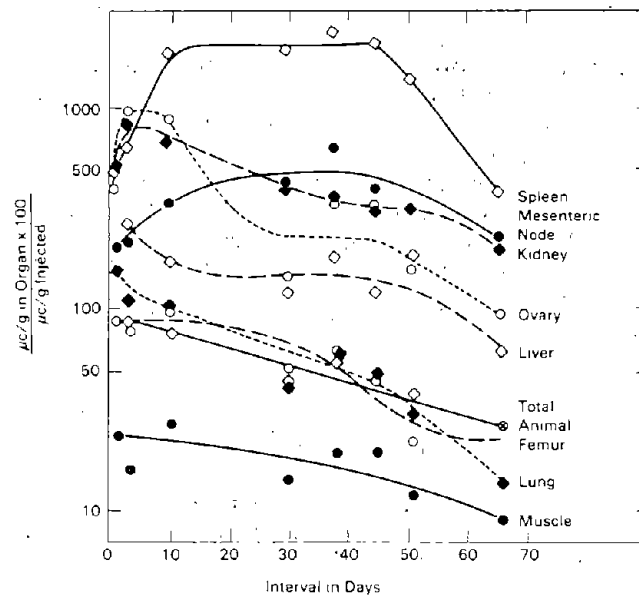


FIGURE 4.4B. Concentration of polonium in the CF1 mouse. (Redrawn from Finkel et al. 1953. Reprinted with permission of The Williams & Wilkins Co., Baltimore, Maryland, copyright 1953.)

speculate on the possibility that ovary might be the critical organ on the basis of its radiosensitivity. However, it remained for postwar work to unravel the possible importance of either ovary or testis in polonium toxicity.

Overall retention in the mouse was comparable to that seen in the rat.

In much of the Argonne (and Rochester) work, microscopic localization in tissue structures was followed by autoradiography as well as by radiochemical analyses.

3. Human Studies

Information on the distribution and excretion of polonium was obtained in humans by experimental injections in hospital patients and by analysis of the occasional accidental contamination.

At Rochester, five hospitalized patients in the terminal stages of lymphatic cancer or leukemia were given intravenous (four patients) or oral (one patient) administrations of small amounts of ^{210}Po . The results are described in chapter 3 of the Fink volume (Fink 1950). The problems of polonium loss in preparing a sterile solution, the inadvertent use of glass urinals, and other technical problems are given in sufficient detail to evaluate the results.

The subjects were:

1. male, generalized lymphosarcoma, i.v. injection of 22.6 μCi at pH 7.6;
2. male, acute lymphatic leukemia, i.v. injection of 11.3 μCi , pH not given;
3. male, chronic myeloid leukemia, i.v. injection of 12 μCi at pH 7.0;
4. female, chronic myeloid leukemia, i.v. injection of 8.6 μCi at pH 7.0;
5. male, chronic myeloid leukemia, oral administration of 18.5 μCi in 2 ml of 0.3 N acid with tap water.

Case 2 died on the sixth day from his far-advanced cancer, and tissues were obtained at autopsy for measurement of polonium concentration. Other subjects lived for longer periods, and excreta were collected for as long as seventy days in Case 3. No other tissue samples became available in this series.

A comparison of relative polonium concentrations in the tissues of Case 2 to rat and rabbit indicated much more in bile and liver, a little less in kidney and in blood cells, and the other tissues were not markedly different from the animal data. Since the information for man came from only one case, very ill, and the polonium was present for a very short period, the Rochester group felt constrained to say no more than that the tissue distributions in man "indicate fairly close similarity between the human, the rabbit and the rat" (Fink, p. 130). The same applied to the excretion results. However, it did appear that the polonium concentration in blood fell more slowly in human plasma and more rapidly in human cells and whole blood than in the rat.

The one case given polonium orally indicated that uptake from the gut was less than 10%. Excretion was largely by the feces as in the rat, remaining at over ten times the rate in urine, even as long as 230 days after the administration. After intravenous doses, it was always from ten to twenty times above urinary excretion.

Kidney clearance of polonium was estimated from the collection of excretion data on these cases. It was surprisingly low in comparison with similar metals such as arsenic and selenium.

Absorption through human skin did not exceed 2% of the dose per day. Red cell uptake in vitro was slower than in vivo.

Comment on Human Studies. Like the human studies on uranium described in chapter 2 and those on plutonium to be cited in chapter 7, these experimental injections would be almost impossible now. The published results do not delve into matters of informed consent. But it seems likely that these individuals knew their prognosis well and if asked would have been glad to help out with the war effort.

Confirmation of the experimental work in humans with information from cases of accidental exposure did not take place until postwar, partly because of the tight security on information concerning polonium.

C. Toxicity of Polonium

1. Acute Effects—Lethality

Toxic doses of polonium were given to rabbits in the very early experiments of Fernau and colleagues (cited in the Fink volume, chapter 7) and of the Lacassagne group cited there also. Chapter 7 of the Fink volume both summarizes these works and gives much detail. By translating the electrostatic units used by Lacassagne to microcuries, Boyd, Silberstein, and Fink (1950) estimated acute lethality at about 50 $\mu\text{Ci/kg}$ for twenty days. By interpolation of their graph (figure 7.2 of the Fink volume), the similar figure for thirty-day lethality would be about 30 $\mu\text{Ci/kg}$. These cannot be regarded as true LD_{50} ^(a) values because of the paucity of data, but they give the general range of effectiveness.

As a part of the large comparative study of polonium, plutonium, and radium at Rochester, discussed in chapter 7 of the Fink volume, Boyd, Silberstein, and Fink (1950) gives details of the polonium series. The comparative toxicity results were graphed as figures 7.14 and 7.15 in chapter 7 of that book. By a plot of mean survival time against dosage, Boyd calculates the LD_{50} for twenty days at 130 μCi per kilogram body weight in the pilot experiment.

The much larger "simultaneous study" (Fink 1950, chapter 8, especially Boyd and Fink, part 6) did not provide data that could be analyzed by formal procedures for the LD_{50} , but an approximation could be made from median survival times plotted against median dosages. Here median survival time of twenty days was associated with a median dosage of about 43 $\mu\text{Ci/kg}$. The similar figure for thirty-day median survival time was about 35 $\mu\text{Ci/kg}$. The authors give (in their table 8.9) 27 $\mu\text{Ci/kg}$ as the 50% lethal dosage of polonium for forty days. All of these are considerably lower than the figures derived from the smaller pilot experiment and are probably more reliable. Also, they agree better with the figures derived from Lacassagne's work with the rabbit.

The Chicago work by Finkel et al. places the LD_{50} , thirty days, of intravenous polonium in the CF1 female mouse at "between 30 and 40 $\mu\text{Ci/kg}$." The figure from their graph (figure 3, Finkel et al. 1953) is 36.5 $\mu\text{Ci/kg}$. Such agreement with the work on the rat may be fortuitous, but let us accept it at face value.

Because of the high specific activity of polonium, these acutely toxic doses represent minuscule weights. The 50% lethal dosage at twenty days is only 0.0096 $\mu\text{g/kg}$, and at forty days only 0.0060 $\mu\text{g/kg}$. Similar figures for ^{239}Pu are 1,320 $\mu\text{g/kg}$ and 860 $\mu\text{g/kg}$ and for ^{226}Ra they are 2,100 $\mu\text{g/kg}$ and 1,140 $\mu\text{g/kg}$. Polonium is obviously a much stronger candidate than plutonium for the title of

(a) The lethal dose to 50% of the animals.

"most toxic element known to man" in terms of acute lethality on either a weight basis or an activity basis.

2. Acute Effects—Pathology

The careful documentation of pathological changes in the Rochester experiments with radium has already been reviewed in chapter 1; those with plutonium are reviewed in chapter 7. The changes after polonium were so much like those after acute doses of whole-body x-radiation as to make any extensive description redundant. The testes and hematopoietic organs showed the most change in the pilot experiment (Metcalf, Casarett, and Boyd 1950). In the larger simultaneous experiment, detailed clinical observations preceded the presentation of pathology (see chapter 8 of the Fink volume). Reduction in spleen size occurred at lower doses of polonium than of plutonium or radium, while very few growth abnormalities occurred in liver. Detailed histopathology was done in this experiment and reported by Casarett, Metcalf, and Boyd (1950). Again the changes were principally manifested in gonads and hematopoietic organs. They involved hypoplasia, atrophy, and hemorrhage. The same types of change appeared in other organs but to a lesser degree. The authors considered only animals dying in periods up to one hundred days after injection and, thus, the work can be considered acute or subacute. Longer-term effects, including the development of cancer, will be described in later sections.

Formal hematology studies, as contrasted to pathology, were done for polonium only in the simultaneous experiment.

3. Long-Term Effects

In the Rochester work, the primary long-term effect studied carefully during the war was lethality out to 300+ days in the pilot experiment and to about 120 to 160 days in the simultaneous experiment. To a lesser extent, they report weight gain or loss. The comparative toxicity is taken up in detail in our chapter 7. Suffice it to say here that polonium persisted in being the most effective of the trio, polonium, plutonium, and radium. At 100 days, it exceeded radium by a factor of eighteen on a per microcurie basis, or 82,000 on a per microgram basis. At 300 days it was, however, only a factor of two higher than radium and the same as plutonium on an activity basis. This change in relative effectiveness, while quantitatively not fully reliable because of the small size of the pilot experiment, is seen also in postwar studies, which we will review presently.

The Chicago work on long-term effects was not reported until 1954.

IV. Research on Distribution, Excretion, and Effects of Polonium in the Post-World-War-II Era

A. Introduction

Postwar work on polonium followed two quite distinct pathways. The first, which is the subject of this section, was a continuation and extension to longer times and greater depth of the type of work done during the war, i.e., distribution, excretion, and effects of experimentally administered doses in animals. The second area concerned polonium in the environment, especially its presence in tobacco and its possible contribution to the genesis of lung cancer in people. This is the subject of section V.

Three American laboratories made the major contributions to the extensions of the war work: ANL, Mound Laboratory,^(a) and the University of Rochester Atomic Energy Project. In addition, a large effort was mounted in the USSR and the United Kingdom, and German laboratories entered on specific problems.

Production of polonium in large quantities declined markedly in the postwar era, and the work was thus less pushed by practical needs. Nevertheless, potential for large contaminations with polonium appeared in the proposed use of molten bismuth in some advanced design reactors.

The ANL work consisted essentially of completing the long-term mouse experiment and reporting it in an ANL report. The Mound Laboratory work considered distribution, excretion, and effects in both animals and man. Results were released primarily in Mound Laboratory reports, although there was a summary by Spoerl and Anthony (1956) as a chapter in the monograph edited by Moyer, Gnagey, and Rogers (1956)^(b) and a few open literature publications, particularly from the Atoms for Peace Congress. The Rochester work, while issued piecemeal as project reports, was gathered together in a single publication as a supplement to the journal, *Radiation Research* (Stannard and Casarett 1964),^(b) termed hereafter the "Polonium Supplement." The USSR work is available in the AEC Translation Series as a useful and succinct monograph (Moroz and Parfenov 1972a).

B. Solution Chemistry and Radiocolloids

The postwar work not only extended the periods of observation, went to lower dosage levels and chronic administration modes, but delved much more into the physicochemical reasons for the peculiarities of distribution and excretion uncovered. The first five papers of the Polonium Supplement dealt with the colloidal properties of polonium in solution, its binding to biological entities, particularly blood constituents, and the bearing of these on biological behavior. The Mound Laboratory looked at the association of polonium with blood as described in several quarterly reports and a publication by Campbell and Talley (1954).

Both sets of results showed that the polonium in the blood is associated primarily with the red cells, and in them it is attached to the globin portion of the hemoglobin molecule (Thomas 1964; Campbell and Talley 1954). Work on the behavior of polonium as a colloid (Morrow et al. 1964a; Thomas and Stannard 1964c) helped to explain its behavior in vivo (Thomas and Stannard 1964b).

(a) In 1945, the MED concluded that the Dayton Project should become a permanent facility to be operated by the Monsanto Chemical Company. The site for the new installation was on the edge of Miamisburg, Ohio, near the site of some ancient Indian mounds about twelve miles south of Dayton. On this basis, it was named "Mound Laboratory." Some biomedical work was probably begun even before completion of the new facility in 1948-1949. But all of the reports are sufficiently postwar that their review is more appropriate for this section of the chapter.

The new "Mound Laboratory" began by processing polonium for neutron and alpha sources. But in later years, it turned more to production of plutonium sources, especially ^{238}Pu as used in space vehicle power sources and other applications including biomedical ones. The Biology Division was disbanded sometime in the late 1960s, but Health Physics has, of course, continued.

(b) The tables of contents of these two monographs are given as notes 1 and 2 at the end of this chapter.

The markedly increased amount of polonium associated with red blood cells after oral administration seemed also to find a likely explanation. It appears that the form combining with hemoglobin in the red cell is essentially monomeric. The absorption from the gastrointestinal tract to blood is much more in monomeric form than after direct intravenous injection. Conversely, the polyatomic groupings, either present in the injection solution or formed by the rather sudden high concentration of polonium introduced intravenously, are picked up by elements of the RES.

Autoradiographic studies by Gallimore, Boyd, and Stannard (1954) confirmed the microscopic presence of large aggregates of polonium in cells and tissues after intravenous administration and traced their gradual dissolution with time. L. J. Casarett (1964a) showed that these aggregates were not present after oral administration. He pointed out also that aggregates, when present, were found principally in the alveolar walls of the lung, the Kupffer cells of the liver, the red pulp of spleen and other constituents of the RES. Nonaggregated polonium maintained qualitatively the same distribution, irrespective of the route of administration, whereas aggregated polonium distribution was quite sensitive to route of administration, form administered, and even the size of the dose.

Lanzola, Allegrini, and Taylor from the United Kingdom (1973) examined the subcellular distribution of polonium over periods of up to forty-seven days after various routes of administration. They conclude that it binds rather nonspecifically to protein, a conclusion also drawn by the Rochester workers from electrophoresis studies in vitro (Thomas 1964). The U.K. investigators found some evidence that the sulfhydryl group of cysteine may be an important binding site. They also suggest that at low concentrations, such as those attending occupational exposures at or below the maximum permissible level, the complexing agents in blood and tissues should be present in sufficient quantity to wipe out differences in form caused by different routes of administration. While logical, there has not been experimental verification of this point, since all the work we are reviewing was at doses well above the maximum permissible occupational exposure.

Feldman and Saunor (1964) worked out the filterability of polonium in the presence of various polycarboxylic and amino acids and concluded that in tracer concentrations any polonium carried in the blood in diffusible form would be bound to citrate (about 75%) and bicarbonate (about 20%), with the rest bound to other small moieties. Being physical chemists, they were especially unhappy with the lack of reproducibility in their preliminary work and turned to "homogenous pH adjustment" instead of bringing acid solutions to neutrality by adding droplets of strong sodium-hydroxide solution. The homogenous pH adjustment was achieved by operating in urea plus ammonium chloride, plus heat. Solutions prepared by this means showed little change in filterability at different polonium concentrations, while solutions prepared by the conventional method did show such an effect of concentration.

These phenomena led the editors of the Polonium Supplement to append a footnote to the Feldman-Saunor paper as follows:

Editorial Note: It is unfortunate that many long-term animal studies had been started, using older techniques, before the findings described in this paper were available. Refinements in solution preparation might have reduced the range of biological observations. Yet this is only conjecture, and it is equally likely that such refinement would have had little influence on in vivo results. Also in inhalation experiments, and in many experiments using other routes, the initial solution was

not neutralized before entry. Especially noteworthy is the fact that tissue distribution and excretion were not measurably different, nor was the range of values different after intravenous injections of acid solutions as compared to neutralized or partially neutralized solutions. Thus the total history of the solution before and after injection must be considered, as was pointed out by the authors in this paper, but large differences in biological end-point results may not necessarily follow any given variation of solution handling or history. In each of the papers that follow, the handling of the injection or exposure solution will be spelled out. (Stannard and Casarett 1964, p. 47)

There is no question but these phenomena are applicable, to some degree at least, to all work with injected radioisotopes. The history of the solution should be both known and controlled.

These phenomena, plus the possibility of differences between tracer levels and toxic levels of elements such as polonium, raise questions about the validity of details of some of the work done, both during and after the war. However, since we are interested in both, the question is not so much one of validity of results as careful scrutiny of the conditions before making broad generalizations or extrapolations. Very possibly phenomena such as these may underlie many instances attributed to "biological variability."

On the other side of the coin, it may be the unaggregated material that contributes most of the dose (L. J. Casarett, 1964a; Stannard and Casarett, 1964, p. 401). This fraction is less influenced by the many factors impinging upon it than the more spectacular aggregates.

Three paragraphs from p. 401 of the Polonium Supplement bear on these considerations:

An important contrast in physical state in vivo is seen by varying the route of entry. The larger aggregates characteristic of early times after intravenous administration do not appear in blood or tissues after oral administration. They are seen in the gut, however. Thus, the contribution of the large aggregates is entirely absent after oral administration except for the gut wall itself. After inhalation, aggregates can be found in lymph nodes, lung, upper respiratory tract, gut, or phagocytic cells, but almost never in other tissues.

In a sense the presence and behavior of these aggregates is analogous to the "hot spots" much discussed in work with the bone-seeking α -particle emitters. However, the aggregates do not persist as such for long. The source of "hot spots" is more referable to biological concentrating mechanisms—for example, concentrations of macrophages, "whirlpools" in the bronchiolar ciliary epithelium, and concentration in lymph nodes—rather than to processes at the submicroscopic level as alleged for the accretion of radionuclides in bone. Thus, the analogy may actually be of little significance.

Furthermore, even the apparent localization seen may contribute less to the total radiation dose than might be predicted from casual observation. L. J. Casarett points out that the single atoms or small groups of atoms, ubiquitously present in the tissue sections studied, are much less dramatically emphasized in the autoradiogram than the large aggregate. Careful track counts indicated that less than 20% of the total activity appearing in the autoradiogram was contributed by polonium in the larger aggregates. This was in tissues of an animal receiving "neutralized" solution intravenously and hence having a maximum of larger aggregates. Since the aggregates are disorganized within a few days in vivo, we must conclude that the "hot spot" problem is probably not of large significance, nor is this aspect of the physicochemical state of the entering solution the primary factor in determining dose distribution except during the initial hours after administration. (Stannard and Casarett, 1964, p. 401)

The work of Moroz and colleagues (1971, 1972) in the USSR also examines the importance of radiocolloid formation and reaches similar conclusions.

C. Distribution and Excretion

The principal centers of activity postwar were Mound Laboratory, Rochester, and the USSR.

Effects of the route of administration were examined in depth at both Rochester and Mound Laboratory (Davis and Stevenson 1954; Stannard 1964; Morrow et al. 1964b; Thomas and Stannard 1964a; Morrow and Della Rosa 1964; Berke and DiPasqua 1964; L. J. Casarett 1964a,b; Smith et al. 1961). The routes were intravenous, oral, intratracheal, inhalation, and a direct introduction into the isolated intestinal loop in the cat. While the rat was still the principal test animal, cats, dogs, and rabbits were included for spot checks.

On the whole, the differences among routes were not unlike those noted in the wartime work, but the experiments were much larger and longer in general.

One of the earlier postwar publications on distribution and excretion concerned inhalation of a polonium aerosol by dogs (Smith et al. 1961). The radioelement was inhaled on a sodium chloride vector aerosol, and the observations went to about 150 days. Over 60% of the inhaled polonium was deposited in the animal, mostly in the lung. It left relatively slowly, going down to 32% to 49% of the total body burden in lungs by thirty days, and thereafter leaving with a biologic clearance half-time of about thirty-six days. Lung content and excretion seemed to follow single-exponential-loss kinetics, while whole-body-burden loss required a two-phase equation. Curiously, the pelt increased temporally in content relative to other organs, and the polonium seemed to be in the hair follicles. This observation was never followed up.

A useful series of equations is given for calculating radiation dose, body or organ burden from blood or excreta contents.

The bulk of the distribution and excretion work employed the rat. A summarizing comment on the results of long-term studies at Rochester is given in the following excerpt from the summary chapter in the Polonium Supplement:

Long-Term Studies of Distribution and Excretion

To understand long-term biological effects, it was considered essential to study the pharmacodynamics of the radioisotope over equivalently long periods. Therefore, two massive experiments were undertaken; one concerned the fate of a single intravenous dose for as long as it could be followed (445 days), the other a multiple-dose regime carried for the life span of the animals.

The single-dose experiment demonstrated marked differences and some points of general similarity in metabolism of polonium in different organs and tissues as a function of elapsed time. In all tissues except testis there were two phases of loss—a rapid phase, sometimes exponential with time but frequently continuously variable with time, and a slower phase, usually exponential with time. But the duration of the rapid phase varied from zero to 300 days, whereas over-all half-times ranged closely about 30 days. The duration of the slow phase varied from 150 to 450 days with effective half-lives from 59 to 93 days. Obviously, such a range might allow a large variety of tissue retention patterns, and such is indeed the case. It was possible, however, to group the tissues under three major headings: group I, containing spleen, kidney, liver, lung, lymph nodes, bone marrow, and femur, which has a long rapid phase and thus a fairly rapid total loss; group II containing testis, skeletal muscle, and heart, which has a short rapid phase or none at all, a longer slow phase, and slower average loss; and group III containing blood cells, which held polonium most tenaciously of all tissues ($T_{eff} = 93$ days).

If biological loss only is considered, the differences in tissue binding are further emphasized. The retention half-time for liver is only 11 days, but it is 153 days for testis. The median half-time among tissues for polonium loss is 38 days, in good agreement with the values for the whole body and skeletal muscle.

Obviously such varied kinetics must result in marked changes in relative distributions with time. Many tissues with high concentrations initially—for example, liver—lose isotope so rapidly that they soon contain less than many tissues of initially lower content. This “redistribution with time” is partly an active redistribution, partly only the result of different retention times. After a few months, a very significant fraction of the body burden of polonium is found in blood cells. Their contribution to the radiation dose, which may be quite significant, is discussed later.

The radiation doses to different individual tissues are not those predicted for the average tissue or from initial distribution. (Stannard and Casarett, 1964, p. 405)

Also:

Our long-term multiple-dose experiment demonstrated how wrong extrapolations from single-dose data may be in predicting tissue concentrations over long periods. First, the equilibrium body burden on a monthly dosage regimen was twice the monthly dose, rather than one and one-half times as predicted from single-dose data. The urinary excretion was slower; the effective half-life (whole body) was 40 days rather than 30 days, and the pattern of tissue contents was always more nearly that at shorter times than at longer times after a single dose. This latter relation might be predicted from the fact that an appreciable fraction of the body burden at any given time is from relatively recently acquired doses.

The relative radiation doses to various critical organs with constant body burden are shown in Table II. The contrast between these and the doses after comparable single administration is clear. The cumulative difference is reduced somewhat, of course, by the fact that a considerable fraction of the radiation dose occurs within a few months after a single injection.

Multiple exposures by inhalation were carried out by Berke and DiPasqua, but the time scale was much shorter (10 days) than in the maintained body burden experiments. In this short time no marked contrast was seen between the accumulation and distribution of polonium in tissues predicted from single doses and the concentrations found after multiple exposures. Delayed excretion was considerably more rapid after multiple exposures, however, and the lung clearance could be described by a single exponential function of time rather than by a compound function. The relative blood concentration rises after either single or multiple exposures to a value well above that of spleen or kidney about 2 months after cessation of exposure. This is reminiscent of the contrasts between oral and intravenous entry routes and may represent a gradual release of ‘solubilized’ or ‘ionic’ polonium from reservoirs in lung and tissues of the reticuloendothelial system and gradual release of ions bound to protein. (Stannard and Casarett, 1964, pp. 406-407)

At Mound Laboratory, a multiple-dose experiment of long duration was also carried out (Davis, Rockhold, and Anthony 1954). It used 120 Sprague-Dawley rats that received about $2 \mu\text{Ci/kg}$ of ^{210}Po intravenously at fourteen-day intervals for ten injections. The body burden was approaching equilibrium in the females, but not in the males, by the 139th day. The “constant” body burden approached was about $6 \mu\text{Ci/kg}$, considerably above the equilibrium body burden of twice the monthly dose described for the Rochester-Wistar rats. This may seem logical because the injections were twice as frequent. However, with an effective half-life of about 30 days, the body burden in the Mound Laboratory experiment should have continued to increase. It is possible that the equilibrium level had actually not been reached, or there is some other difference

between the experiments. However, the Mound Laboratory experiment was not designed so much for comparison of metabolic parameters as for eventual effects. Therefore, the authors do not emphasize possible differences in pharmacokinetics. Except for the difference in possible equilibrium values, a review of the data does not indicate significant conflicts with the Rochester experiment.

The ever-present problem of the extent to which the animal data on metabolism can be applied to humans was attacked by Stannard and Smith (1964). They concluded that the differences in distribution patterns are no greater among species than through variation in route of administration, etc. Excretion patterns did seem to be consistently different, with the rabbit excreting more polonium in urine and the dog consistently less. People seem to resemble the rat more than other species in both relative rate and the proportion in urine versus feces.

At Mound Laboratory (Naimark 1948; Svirbely 1949), the effective half-life in humans was estimated from excretion data on workers as averaging 31.4 days. This is, of course, well within the range of effective half-life in the rat. Using data from accidental inhalation exposures, Naimark (1948) calculated an effective half-life in man of 33 days (range 21.7 to 45.5 days).

D. Effects

It is in the area of effects that the postwar work with polonium added entirely new dimensions to our understanding of the biological effects of polonium, of other alpha-particle emitters, and radionuclides in general. They are described well in the literature, so we will be content with examining the highlights.

1. Long-Term Effects Work at Argonne National Laboratory

At ANL, work with the mouse was carried out to 500 days, as reported by Finkel and Hirsch in an ANL report (1954). Low doses (e.g., $0.004 \mu\text{Ci/g}$), which had seemed innocuous in terms of life-span shortening at 300 days, showed definite effects by 500 days. Only doses of 0.0015 and $0.00046 \mu\text{Ci/g}$ failed to shorten life span. (As so frequently occurs, the survival times were even a little bit longer than the controls at these very low levels.) Also, the body weight changes in the $0.004\text{-}\mu\text{Ci/g}$ group became significantly different from controls after 350 days. Using the plotted survival curve, Finkel and Hirsch calculated that one-half of the 30-day LD_{50} would kill 50% of the mice by 125 days, and one-tenth of the LD_{50} would accomplish this in 485 days.

Of greatest interest is the report of cancer incidence in this experiment at Argonne.^(a) Lymphomas were in high incidence at 0.0015- and $0.0009\text{-}\mu\text{Ci/g}$ doses by 250 days. There was a statistically significant increase in malignant bone tumors even at $0.00046 \mu\text{Ci/g}$.^(b) Indeed, the authors conclude that even their lowest dose was not without deleterious effect in the long term.

(a) Increases in tumor incidence were not described in the war work partly because the times were too short and partly because of the orientation of the investigations.

(b) The appearance of bone tumors is somewhat puzzling for a soft-tissue seeker like polonium. The authors do not comment on the phenomenon. It may be speculated that the tumors arose from deposits in the RE elements of bone marrow. The incidence, while significant, is relatively low (maximum 5.9%) compared to lymphoma (maximum about 48%) and miscellaneous soft-tissue tumors (maximum about 30%). It is much lower than for the bone-seeking elements at equivalent points in the life span. All of these incidences were above the control levels, of course.

2. Effects Work at Mound Laboratory

At Mound Laboratory, Spoerl and Anthony (1956) reported acute and subacute toxicity in the Moyer Monograph. The average twenty-day LD_{50} in the Sprague-Dawley rat after intravenous administration was $43 \mu\text{Ci/kg}$ in males and $36 \mu\text{Ci/kg}$ in females. This compares reasonably well with wartime figures for acute toxicity from Argonne and Rochester. The values were much higher by gavage.

In a group of twelve mongrel dogs, the twenty-day LD_{50} appeared to be about $70 \mu\text{Ci/kg}$ body weight. In cats it was $69 \mu\text{Ci/kg}$, and in rabbits it was in the same region. Thus, the rat seemed to be more sensitive. The authors comment that this proved that the rat was an "excellent choice" for the bulk of the work at Mound Laboratory since it was the most sensitive species.

The Mound Laboratory data for chronic toxicity in the rat extended to about six hundred days. It can be seen from figure 4.5, taken from the Spoerl-Anthony work, that median lethal time was slightly shorter than for the controls at all four of the lower dosage levels, but statistical significance was difficult to work out. The authors remark on an apparently greater sensitivity of the male rat, but this may be a quirk of the data because of the great variability in the female life spans.

Tumors appearing in the Mound Laboratory work were all of soft tissue, and occurrence was independent of polonium dose and was the same as in the controls. Thus, it appeared in this work that polonium was not a carcinogenic element, in sharp contrast to the Argonne and Rochester work. However, the incidence in unexposed Sprague-Dawley rats was quite high, and this may have masked any effects of polonium.

In other respects, the Mound Laboratory histopathology results were, in general, similar to those reported from the war studies elsewhere and to the work going on simultaneously at Rochester. Each quarterly report carried an update of their findings, the chapter by Spoerl and Anthony gives a summary, and a special report by Cowden (1952) was devoted entirely to their single-dose histopathological studies. The work involved single doses from 35 to $0.9 \mu\text{Ci/kg}$ with serial sacrifices up to 375 days postinjection. The most susceptible organs to polonium were kidney, gonads, lymphoid tissue, and "blood" (by which I assume they mean the formed elements of the blood).

The Mound Laboratory also did repeated injection series with doses given each month and, thus, just replacing that lost by decay and excretion. This was in addition to the biweekly injection experiment mentioned in the section on distribution and excretion. This was essentially in parallel, but independent of the maintained body-burden experiment at Rochester. The authors concluded that a maintained body burden of $0.01 \mu\text{Ci/kg}$ failed to shorten life span. The pathological changes at higher levels appeared earlier, were more marked, and involved liver to a much greater degree in the multiple-dose regime. All but the liver changes might be expected if polonium behaved like low-linear-energy-transfer (LET) radiation, and recovery could occur after a dose. (The radiation dose was, of course, higher at early times after a single injection.) But as will be discussed in connection with the Rochester work, it appears that there is little recovery from alpha-particle irradiation. Therefore, these differences in pathology must have another explanation. The authors do not discuss possible mechanisms. The large effect on liver is especially notable. The rest of the pathology findings (Cowden and Zipf 1956) are essentially classic radiation effects.

A unique experiment on reproductive function was carried out by the Mound Laboratory group. Noting the diminution in spermatozoa and long oestrus

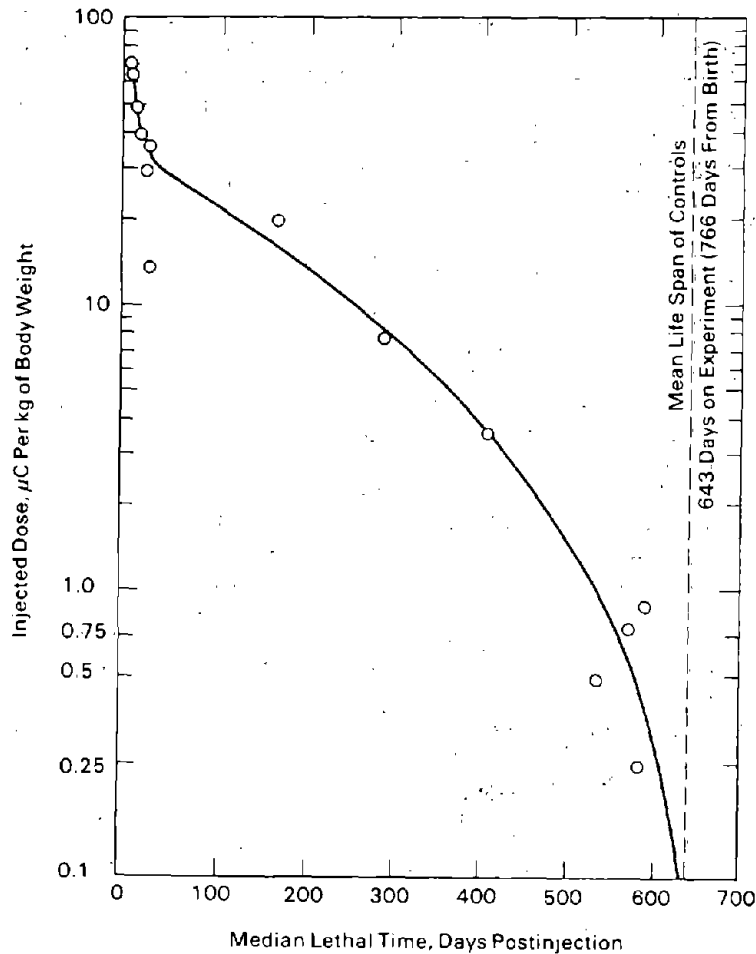


FIGURE 4.5. Median lethal times versus dose in Sprague-Dawley rats receiving ^{210}Po intravenously. (Redrawn from Spoerl and Anthony 1956.)

periods in the animals receiving polonium, they tried some mating experiments. The dose was $14 \mu\text{Ci/kg}$, not a small one. The litter sizes were about the same as normal, or larger, but the number of stillborn was markedly increased, especially if both parents had received polonium.

In a paper delivered at the first Atoms for Peace Conference in 1955, summarizing much of the Mound Laboratory work, Anthony et al. (1956) conclude that the minimum effective single dose of polonium is not less than $0.25 \mu\text{Ci/kg}$, perhaps $0.5 \mu\text{Ci/kg}$ in the rat. A body burden of $0.01 \mu\text{Ci/kg}$ maintained throughout life was considered to be without statistically demonstrable effect on any system (not just measured as life-span shortening).

A final contribution from the Mound Laboratory group, "The Effects of Small Amounts of Polonium on Rats," was seen in manuscript form only, sometime shortly after 1964. All of the authors give new addresses, so it is virtually a swan

song. After reviewing their large long-term studies (results already discussed), they caution against ever trying to set exposure levels for radioisotopes, or potentially toxic drugs, from data covering relatively short periods of time (e.g., only long enough to ensure complete elimination of the agent). In these days of emphasis on low-dose, long-term effects determined experimentally to the greatest degree possible, it is hard to realize that such advice was much needed only two decades ago. It is only now being heeded in some other branches of toxicology.

3. Long-Term Effects Work at Rochester

Work at Rochester on the biological effects of ^{210}Po begun during the war years was extended and amplified primarily because polonium gave a rich opportunity to uncover the effects of alpha particles on soft tissue. The impetus during the war to solve practical exposure problems was reduced. Radon, the other possible choice as a relatively pure alpha emitter, was a very poor second because of its relatively short half-life and the interfering daughter products. The solution chemistry and distribution and excretion work were necessary prologues, but only that. A good half of the 442 pages of the Polonium Supplement (Stannard and Casarett 1964) are devoted to effects work.

It all started with George Casarett's Ph.D. thesis, which reported in depth on a long-term serial sacrifice experiment at four intravenous dosages: 1, 5, 10, and $20\ \mu\text{Ci/kg}$ in the rat. It was, I believe, the first Ph.D. thesis at Rochester to require binding in two volumes. It was first issued as a Project Report (G. W. Casarett 1952).

But let us start with the extensions of acute toxicity work. The earlier figures for LD_{50} were essentially confirmed. A separate study of the effect of *Bartonella muris* infection was undertaken (Scott and Stannard 1954) since there was concern that this endemic infection of the hematopoietic system might influence toxicity. The Rochester colony harbored the infection. The Sprague-Dawley colony at Mound Laboratory did not. Scott and Stannard showed that the LD_{50} values for rats from the two laboratories were essentially the same, so this complication could be checked off. (Nevertheless, efforts were made to eliminate it from any long-term study groups.)

Possibly the most interesting addition to knowledge of acute toxicity of polonium was in the paper by Della Rosa and Stannard (1964). They showed that, despite the rather large differences in tissue distribution brought about by using different routes of administration, acute toxicity was essentially identical. Figure 4.6 illustrates the findings.

Table V of the quoted paper gives median survival times for rat, dog, cat, and mouse, which support the conclusion that acute toxicity is more comparable than the differences in tissue distribution would predict. From this came the postulate that acute toxicity, perhaps also subacute, of substances like polonium, with fairly generalized distributions to tissues, and despite real differences in details of the distribution, was proportional to total body burden. It led also to consideration of the role that the polonium in circulating blood could play in producing effects, which might override differences in dose expected from the tissue contents. It also brought into question the validity of the critical organ concept for calculation of maximum permissible exposures (chapter 16).

A large effort was put into measuring life-span shortening. That from a single dose was analyzed by Blair (1964). He applied the same mathematical formulation that he used previously for external radiation and found it worked for

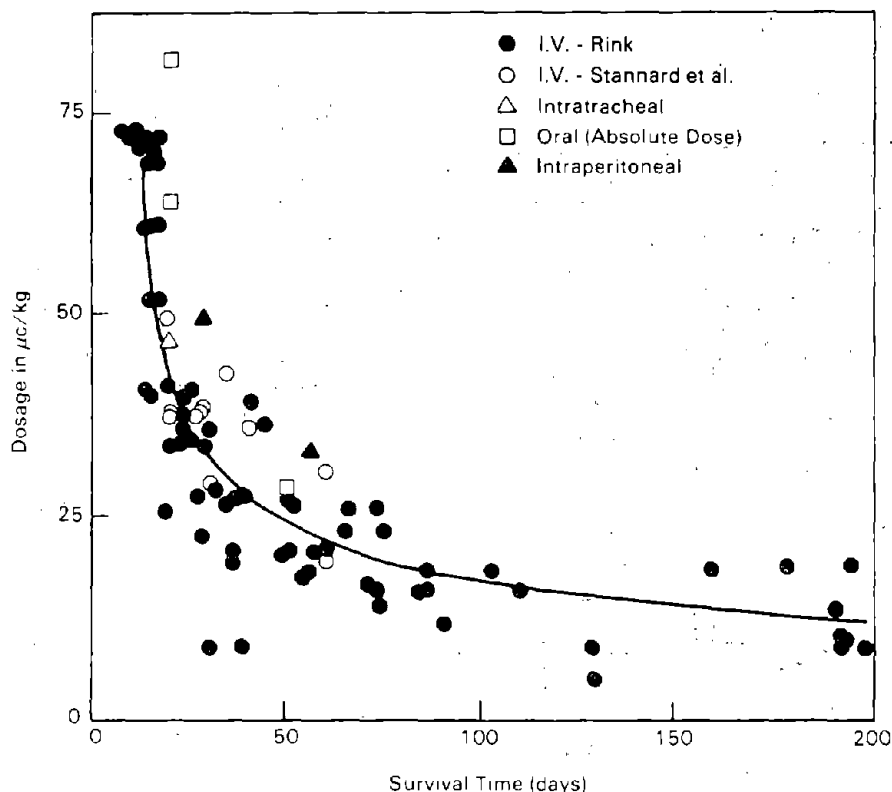


FIGURE 4.6. The mean survival time of Wistar-Rochester rats as a function of polonium dosage. In the case of intravenous injection, the figures on the ordinate refer to injected dose. In the case of all other routes the dosage axis refers to the initial body burden as extrapolated from measurements of actual body burden at time of death in each animal. . . . All experiments are described in the . . . paper except the data from Fink, which are contained in [a] reference. The trend line is the one drawn by Fink to describe the original intravenous studies. (Redrawn from Della Rosa and Stannard 1964. Reprinted with permission of Academic Press, Inc., Orlando, Florida, copyright 1964.)

polonium too. But the fraction of injury defined as irreversible averaged 0.8 for polonium against 0.04 for protracted x rays, an effectiveness ratio of 60. Using already published data in rat and mouse for radium and plutonium, Blair concluded that the life-shortening by polonium, plutonium, and radium stood in the relationship $1 \mu\text{Ci Po} = 0.9 \mu\text{Ci Pu} = 5 \mu\text{Ci Ra}$. The resemblance of these figures to long-term toxicity ratios derived by other means (chapters 7 and 8) is of special interest.

If a large part of the injury brought about by polonium alpha particles is irreversible, then the effects of multiple doses should be quantitatively similar to those from a single dose of the same magnitude. Testing this was one of the chief motivations for the long-term multiple dose experiment. The analysis of Stannard, Blair, and Baxter (1964) confirmed this postulate. Using life-span shortening as the criterion, they found good agreement between the life-shortening

produced by the same total dose attained in a single injection or by multiple injections in the male rat. Also, the shortening was proportional roughly to total dose regardless of regimen. They used several options for expressing dose and mathematical analyses based on the weeks of life-span shortening per microcurie as well as graphical analysis. The female rats showed a tendency for more life-span shortening on the multiple-dose regimen. Also, it was not linear with dose.^(a) No ready explanation could be found for the difference between males and females. However, both sets of data are consistent with the idea that the life-shortening was comparable on the two regimes and that the injury produced was largely irreversible. The highest dose point was somewhat below the line for single-dose data, which might be expected if there were a small fraction of reversible injury. Thus, the fraction 0.8, derived from the single-dose work, may be applicable to the multiple-dose regime. But this requires confirmation. Incidentally, multiple doses of the beta-emitter ⁸⁹Sr were found in work at Argonne to be less effective per unit of dose than single doses, as might be expected from the much lower LET of the beta particle. The relation of this work to other long-term experiments is examined in some detail in the cited publications.

The balance of the Rochester effort concerned histopathology and physiological changes. Only the highlights of the histopathology can be considered here. They are contained in four detailed reports by G. W. Casarett (1964a,b,c,d). These cite earlier publications with even more details. A few points requiring special mention follow.

1. A very clear case was made for the development of arteriolar nephrosclerosis as an overriding mechanism of action. This was accompanied by histopathological signs of hypertension. It was quite dependent on dose, being at a maximum at a dose of 10 μ Ci/kg, almost absent at 1 μ Ci/kg, mild at 5 μ Ci/kg and 20 μ Ci/kg. A dramatic picture of the proliferation of arteriolar endothelium in kidney cortex resulting in sclerosis of an arteriole next to a glomerulus is found in figure 20 of Casarett's paper on the pathology of single doses (G. W. Casarett 1964a).
2. In the absence of generalized arteriosclerosis and attendant hypertension, "the sites and degrees of early and late pathologic effects of polonium corresponded directly with the sites and degrees (concentration and duration) of deposition of the polonium in the body, conditioned by the relative radiation sensitivity of the tissue components" (Stannard and Casarett 1964, p. 415).
3. The factors contributing to death differed to some extent with differences in temporal modes and route of administration.
4. Neoplasms were stimulated in incidence, in shortening of time of onset, and in degree of malignancy. This contrasts with the apparent lack of carcinogenicity in the Mound Laboratory experiments. They were largely sarcomas and carcinomas of soft tissue. The incidence of malignant renal tumors was uniquely high. Leukemia incidence was low, but probably higher than in untreated animals. Bone tumors were not found, in contrast to the Argonne work with the CF1 mouse. Similar increases in tumor incidence, time of occurrence, and malignancy were seen in the long-term multiple-dose experiment, but there were temporal differences.

(a) This is of interest in the light of postulates from the Utah group that protraction of exposure to alpha particles increases effectiveness (Spiess and Mays 1973).

5. The important arteriolar nephrosclerosis, which developed in the single-dose animals, began to develop in the multiple-dose experiment but did not progress even at the dosage level most comparable to a single dose of 10 $\mu\text{Ci/kg}$. Nor did it develop at other dosage levels in the multiple-dose series.
6. No changes attributable to direct effects of polonium were seen in liver on either single- or multiple-dose regimes. The Mound Laboratory work showed extensive liver damage in their multiple-dose series with a body burden of about 6 $\mu\text{Ci/kg}$. This was higher than the highest maintained body burden in the Rochester multiple-dose experiment.
7. After oral administration of an absorbed dose of 25 $\mu\text{Ci/kg}$, there were, of course, effects in the GI tract, and, as might be predicted from the blood and kidney content of polonium, definite changes in kidney. This included nephrosclerosis of the type seen at a single intravenous dose of 10 $\mu\text{Ci/kg}$. It appears that a dose of 25 $\mu\text{Ci/kg}$ absorbed after gavage is equivalent to 10 $\mu\text{Ci/kg}$ given intravenously, and the nephrosclerosis was almost as severe.
8. Changes in testis and ovary would predict definite effects on fertility, but not uncomplicated by other effects that would compromise the reproductive process.
9. Specific changes in lung were not found after intratracheal injection. Three squamous carcinomas of the lung occurred, but it was not possible to prove that these were induced by the polonium. (See chapter 9 for later inhalation studies.)

The final chapter of the postwar research on polonium at Rochester was in the area of functional change.

With microscopic evidence of hypertension, it was logical to make some direct blood pressure measurements. This was done by Sproul, Baxter, and Tuttle (1964) using Long-Evans rats and an indirect noninvasive measurement technique. The experiment was arranged to imitate the condition of the 10- $\mu\text{Ci/kg}$ level in the single-dose Rochester-Wistar rats. There was no doubt about increases in blood pressure taking place as a function of time after injection, beginning at about four months postinjection. They were statistically significant ($P = < 0.01$) at all times after four months, and the increase was enough to be biologically significant as well.

Because of experience with cataract development with external radiation sources, especially those of high LET, these authors also examined the animals with a slit-lamp microscope. Increased opacity began in the injected animals at about six months and reached close to 100% by one year. Control animals developed far fewer cataracts, and these at later times.

Using changes in specific gravity of urine as a test, Sproul and coworkers (1964) showed progressive decreases in kidney efficiency. There was a progressive decrease in specific gravity of urine indicating progressive failure of the kidney to concentrate the glomerular filtrate.

The radiation doses associated with these changes were calculated. They ranged from nearly 5,000 rad to spleen at 350 days to 137 rad to the whole body at 100 days. Thus, we are dealing with phenomena at quite substantial doses.

Tuttle and Baxter (1964) measured reticuloendothelial (RE) function in rats receiving about 7.4 μCi (i.e., an estimated thirty-day LD_{50}) by the uptake of ^{32}P -labeled chromic phosphate. The changes were not large nor considered of much biological significance. These facts fall in line with other indications of

either considerable radioresistance or marked ability to repair damage in the elements of the RES. If one muses that the function of such cells is to rid the body of "foreign invaders," it seems fitting that they should be resistant to toxic agents of various kinds. (They are not always resistant, as we shall see in the USSR work on thorium.)

4. Other Effects Work in the United States

Investigation of the biological effects of ^{210}Po in the United States was, of course, not confined to the laboratories mentioned above. This was particularly true of work associated with possible effects of naturally occurring polonium, as will be seen in section V.

An important addition to the stock of knowledge on effects in the reproductive system came from L. D. Samuels at the Harvard School of Public Health (Samuels 1966). Using the mouse and polonium obtained from England, he gave doses from 10 to 2,000 pCi/g and measured the survival of resting primary spermatocytes. All but the lowest level produced very significant depletion, with gradual recovery. At the two higher doses (600 and 2,000 pCi/g), recovery was slow and incomplete. As might be expected from what we know of alpha-particle effects and the fact that the polonium remains in the testes for a considerable time, the effects were greater and less reversible than from doses of x rays. The local doses were calculated, and the minimally effective one was about 3 rem.

Interest in polonium continued at the Harvard Laboratory in Little's work that concerned primarily effects in the lung. This will be considered in chapter 9.^(a)

E. Work Abroad on Distribution, Excretion, and Effects of Polonium

1. USSR Work

The rather considerable effort in the USSR has already been cited (Moroz and Parfenov 1972a). A shorter but still quite complete version is found in a later review (Moroz and Parfenov 1972b). Because of space limitations and the mission of this book, only very brief consideration can be given to the results.

On the whole, their findings dovetail very nicely with the work done in U.S. laboratories. In many chapters of Moroz and Parfenov (1972a), the results from Rochester are considered along with their own, and the open literature work of Anthony is quoted. The bibliography contains 417 references, a plurality of them work in the USSR. This gives a notion of the extent of their interest in polonium.

There is much more work with the dog than in U.S., British, or German studies. The acute LD_{50} for twenty days is $0.05 \mu\text{Ci/g}$ ($50 \mu\text{Ci/kg}$) and for thirty days $0.03 \mu\text{Ci/g}$ ($30 \mu\text{Ci/kg}$). These indicate sensitivity to acute damage in the dog comparable to that of other species. They arrive at a minimally effective dose of about $0.01 \mu\text{Ci/kg}$ comparable to the "no effect level" arrived at by Anthony et al. They quote work showing that the reduction of life span is linearly related to dose.

(a) Work done on possible therapeutic removal of polonium will be dealt with in the chapter on therapy. Aspects such as its use for detecting deposits of ^{210}Pb have been considered along with the uranium mining problems in chapter 3.

Clinical observations in all species are reported in depth. There is much more emphasis on changes in the nervous system, the endocrines, immune system, and the general stress syndrome than in the postwar American work. While the wartime American work paid more attention to general pathophysiological effects than did postwar research, the USSR studies went further than any. There is a full chapter on the reaction of the sympathoadrenal system, on changes in function of the adrenal cortex, on electrolyte metabolism, and much detail on electrocardiographic changes, the coronary circulation, and the "reactivity" of the cardiovascular system. It is not easy to separate out which of these many functional changes were specific to polonium and which to the generalized radiation sickness induced by the fairly high doses of polonium administered. Perhaps it is not important to make such a distinction anyway.

Decreases in blood pressure were noted in rabbits soon after polonium administration. The observation periods were much too short to allow development of the hypertension seen in the rat at Rochester associated with nephrosclerosis. The Moroz monograph devotes some space to long-term effects, but the cited works are mostly American. The USSR work describes increased incidences of lymphomas, lung cancer, and neoplasms of the mammary and sex glands in mice and rats. Kidney tumors were described in rats receiving doses of 5 and 2.5 $\mu\text{Ci/kg}$. The unique kidney lesion described by G. W. Casarett (1964a) was not remarked upon. This is not surprising since its incidence is limited to a narrow range of doses.

Clearly, the quite extensive USSR studies with polonium possess many features not so fully investigated in American or British work. The primary findings are, in general, similar, as they had to be. There are occasional differences in fact or interpretation (e.g., effects in brain). But when these do occur they are pointed out, and they are not major.

2. Other Work Abroad

Despite much attention to alpha emitters in the postwar years in England, France, and Germany, relatively little work was done on polonium *per se*, except for its appearance in the environment and various aspects of radon daughter investigations. Even in France, with the impetus given by the Curies and Lacassagne, biomedical interest went to other elements emitting alpha particles.

Some work was done on chemical binding in tissues at the Institute of Cancer Research in Sutton, Surrey, U.K., with collaboration from Italian investigators at Pavia (Lanzola, Allegrini, and Taylor 1973). A symposium on all aspects of polonium metabolism and effects was held also at Sutton, Surrey in 1970, with an internationally derived set of participants. The proceedings of this excellent meeting were never published, and we have only a copy of the program and abstracts for a permanent record (U.K. Polonium Symposium 1970).

On the whole, the bulk of the work of the type described thus far in this chapter was done in France, the United States, and the Soviet Union.

V. Polonium in the Environment, Especially in Tobacco

A. Introduction

It would be expected that measurable amounts of polonium would exist in the environment as a result of decay of uranium and radium in the earth's crust,

and from radon and its daughter products in the atmosphere or water. Furthermore, it would have many opportunities to enter the food chain and be incorporated in the bodies of animals and man. The accumulation of ^{210}Pb in bone by development in vivo from deposited radium or radon daughter products can lead to production of polonium in situ, and excretion in urine, which could conceivably be used as a measure of radon exposure (Sultzer and Hursh 1954).

A substantial amount of research has been done both to measure the amounts present in various natural environments and to gauge increments due to the activities of man. Unlike the experimental research we have been discussing, this work consists primarily of measuring how much is present, in what form, the influence of various factors on the form and amount present, and then speculating on the possible biological significance of the amounts found.

While we are saving much of our discussion of environmental research for the discussion of fallout, work around nuclear installations, and the development of the field of "radioecology," a brief review is pertinent here while we are engaged with polonium and its effects. No particular laboratory can be singled out for separate presentation because the work on naturally occurring polonium was usually part of a broad spectrum of such activities in various institutions. The most complete discussions appear in the USSR Monograph (Moroz and Parfenov 1972a), a report by the National Council on Radiation Protection and Measurements on natural background radiation (NCRP 1975),^(a) and several reports from the Scripps Institution of Oceanography of the University of California at La Jolla (Folsom, Wong, and Hodge 1972).

B. Natural Occurrence of Polonium

Concentrations of ^{210}Po in air, rain water, plants, marine plankton, drinking water, food products, and in animals and man are reported in detail by Moroz and Parfenov (1972a,b). They cite, in addition to voluminous USSR sources, work by Holtzman at Argonne National Laboratory, Blanchard from the U.S. Public Health Service, Hill in the United Kingdom, Globel and Rajewsky in Germany, and others. The "natural intake" may be direct or indirect by production of polonium in vivo from precursors.

The largest natural terrestrial sources are inhalation of aerosols of ^{210}Pb - ^{210}Po , plus ingestion of polonium in drinking water and food. Ingestion of some sea-food products gives higher than average intake because of the accumulation of polonium in the marine trophic sequence (Folsom, Wong, and Hodge 1972) to be discussed presently.

The natural burdens in the tissues of man are in the range from a few picocuries per kilogram to a fraction of a picocurie. Hill (1965) reports, for example, 7 to 10 pCi/kg in normal human liver tissues, and this is among the highest concentrations found. The metabolic balances of ^{210}Pb and ^{210}Po were measured in twelve men maintained on a metabolic ward by Holtzman et al. (1974) at Argonne National Laboratory. Mean levels of dietary intake were about 1.6 pCi/day over a period of five months. Excretion exceeded dietary intake by a small amount, being 0.27 pCi/day in urine and 1.9 pCi/day in feces. Atmospheric concentrations were not sufficient to make up the balance, but cigarette

(a) Extended and confirmed by a recent NCRP report seen in draft form (NCRP 1986).

smoke could (see later section). Thus, none of these levels of natural occurrence in man is high in an absolute sense. Overt biological effects would not be incontrovertibly expected from such concentrations in themselves.

An interesting exception occurs in the far North. In Lapland and Alaska, the intake by man can be well above average because of the lichen-reindeer-man food chain. Lichens accumulate large amounts of many radioisotopes simply by virtue of their long life (estimated at hundreds, even thousands of years), and polonium appears in them in concentrations many times those seen in ordinary grass and other plants. Since reindeer and caribou feed largely on lichens part of the year, any residents of the far North consuming much reindeer or caribou meat have both higher intakes and higher body burdens of polonium. The accumulation in lichens is tenfold that of the usual plants of temperate latitudes. Hill (1965) estimates that the concentration of ^{210}Po in reindeer skeleton is twenty times the level in cattle in temperate latitudes. (Remember that radiolead is in skeleton, and the polonium can be generated in situ from it.) That in reindeer muscle is higher by a factor of two. Kauranen and Miettinen (1967) estimate the concentrations in tissues of reindeer at ten times those in elk, which do not feed on lichens. Thus, sometimes the factor by which polonium concentrations in the bodies of human inhabitants of the far North who eat reindeer and caribou meat exceeds that of those from other areas by as much as one hundred (work of Mayneord and Hill; Hill; Holtzman; the Miettinen group and others cited by Moroz and Parfenov 1972a).

The NCRP report (1975) presents estimates of dosages in man from a large number of internally deposited nuclides acquired naturally. It is of interest that the ^{210}Po dose contribution (in millirem) to gonads, osteocytes, and Haversian canals from cortical bone deposits of the precursor ^{210}Pb are easily well ahead of several radium and uranium isotopes and ahead of both ^{222}Ra and ^{226}Ra . Likewise, the calculated "effective MeV" for ^{226}Ra , ^{228}Ra , and the ^{210}Pb series is always maximal for the polonium isotopes. The calculated doses from naturally occurring deposits are of the order of 60 mrem/yr maximum.^(a)

Naturally, all these figures for terrestrial amounts of polonium are subject to geographical variations, especially in consideration of some of the areas of high background radiation. Also, differences occur as a function of factors causing variations within a given environment.

In the marine environment, the situation is quite different. The group at the Soledad Marine Radioactivity Laboratory of the Scripps Institution of Oceanography, La Jolla, California, became engaged with studies of the accumulation of radionuclides from fallout in the oceans of the world and in representative organisms. They placed special emphasis on the Pacific area.

As a corollary, they, and other oceanographic groups, investigated the concentrations of naturally occurring elements. The Scripps researchers became convinced that the alpha emitters had been neglected and made extensive studies of ^{210}Po , in part as a surrogate for plutonium. They were well rewarded for their efforts.

(a) The draft NCRP report cited in the footnote on page 230 calculates annual dose equivalents from ^{210}Pb - ^{210}Po contained in the body as 14 mrem to soft tissue, 60 mrem to bone surfaces, and 14 mrem to bone marrow. Potassium-40 is calculated as contributing 19 mrem/yr to soft tissue, 15 mrem/yr to bone surfaces and to bone marrow. Doses from naturally occurring ^{222}Rn are given as 11 mrem/yr to each tissue named.

Quite high concentrations of polonium were found in a variety of marine organisms, both ones living near the continents where the precursors of polonium exist and in organisms collected from the open ocean. In the albacore tuna, a digestive organ (not canned for human consumption), the pyloric caecal mass, went as high as 79,000 pCi/kg wet weight. This is over two million times the usual concentration in surface sea water. The liver for the common dolphin ran about 4,000 to 11,000 pCi/kg, the lantern fish viscera from 17,000 to 26,000 pCi/kg, and many mollusks showed concentrations in the soft tissues in the same range, although others were much lower. Folsom and coworkers calculated "concentration factors" (the concentration in the organism or tissue of the organism compared to that in surface sea water), a subject we will see more of in chapters 11 through 13, for seven species. The factors are from high to very high. In terms of calculated radiation dose, the authors estimated the maximum (caecal tissues of the albacore tuna) at about 8 rad/yr. If we use a Quality Factor of 10, or the currently accepted 20, the resulting dose is 80 or 160 rem, both of which are well above the current maximum allowable exposures even for occupational situations and far above the permitted population exposure level. Fortunately, the viscera are seldom eaten by man.

A lesson in the need for care in evaluating tissue doses from alpha emitters came from work with the giant kelp (a brown alga). This plant grows luxuriantly just beyond the surf line near San Diego, La Jolla, and similar areas. It is harvested to make agar. Wong, Hodge, and Folsom (1972) found very high concentrations of polonium in this plant. But most of it was on the outermost thin layer of the antlers and bladder tissues. The thickness of the layers is such that only a small fraction of the alpha dose would reach the inner tissues. Much depends on the importance to biological function of the outermost tissue layers. Plutonium was also measured in this work. It showed the same tendency to concentrate on the outer layer but to a much lesser degree. Also, there was much less plutonium present in all tissues.

The high concentrations in areas such as the pyloric caecal mass of pelagic fish may have been partly in the contents and not in the walls of the organ. There seems little doubt that the mechanisms of polonium accumulation are entirely different in the case of these fish than in the giant kelp.

A general survey of midwater fish of the eastern Pacific was carried out by the Scripps group (Hoffman, Hodge, and Folsom 1974) using specimens collected by the Naval Underwater Research and Development Center, San Diego. Most of the polonium was found in the digestive tract, indicating it entered via the food. It seems likely that the concentration process is occurring all along the trophic ladder. Samples of bottom-living fish, which might be near radium deposits on or just below the sea floor, were expected to show high concentrations of polonium. They were moderately high but not enough to pinpoint bottom radium as the source of marine polonium. Furthermore, much of the polonium seemed to be unsupported by ^{210}Pb . We must conclude that the high concentrations in marine organisms result from a catenary series of concentrating steps. But exact details need further examination. The factor between the liver of man and albacore liver is about one thousand, not so large, naturally, as the comparison to sea water, but still a phenomenon to be reckoned with.

C. Polonium in Tobacco

The marked increase in incidence of lung cancer and the role of smoking in its causation has naturally turned attention to the identification of the carcinogenic

agents in tobacco. As evidence developed in laboratory research (chapter 9) that alpha emitters were potent carcinogens to the lung when inhaled as aerosols of plutonium or of polonium, and the dreary saga of the uranium miners unfolded (chapter 3), attention turned to a possible role of naturally occurring polonium in the production of lung cancer in smokers.

In the United States, it was probably Radford, then researchers at the Johns Hopkins University School of Public Health, who diverted attention from the tars in tobacco to its content of radioisotopes. Radford and Hunt (1964) calculated the dose to bronchial epithelium from ^{210}Po inhaled on particles in cigarette smoke. The minimum dose estimate was 36 rem as a result of smoking two packs of cigarettes per day for twenty-five years. This was recalculated by Skrabale and colleagues (1964) using a different mathematical model (that of the International Commission on Radiological Protection [ICRP]) and a much lower figure appeared likely. There was further discussion of the need for better models by Radford and coworkers in the same issue of *Science* (Radford, Hunt, and Little 1964). Biases began to develop among environmentalists and radiation biologists. Actually, Radford was not inclined to push polonium as the causative factor, but he emphasized that "if polonium in smoke is found not to be involved in bronchial carcinogenesis, this will greatly strengthen the view that exposure to chronic low doses of radiation is not hazardous. On the other hand, proof that chronic radiation exposure is involved in production of cancer would have obvious significance." In 1966, Rajewsky and Stahlhofen considered the doses far too low to be causative agents. And so it went. To a degree, this pushed the story of polonium in tobacco into the raging controversy on the effects of low levels of radiation and made it front-page news.

Further work was done in several laboratories. It became clear that the polonium content of tobacco could vary considerably in different types of tobacco and in different locations. It also seemed that the polonium content was largely foliar, which indicated deposition from the air rather than uptake from the soil. Lead-210/polonium-210 ratios were used to determine how long the insoluble particles from cigarette smoke remained on bronchial epithelium (Radford and Martell 1976), a much needed parameter. The polonium content of many plants was measured. There were not large differences in initial content. But Martell (1974) found that ^{210}Pb activity of tobacco was transformed into insoluble particles by the curing process. Also, the small trichomes on the surface of the tobacco leaf entered the smoke stream and were deposited in the lungs. Here they produced high local alpha irradiation sources by the ingrowth of ^{210}Po . Indeed, the same trichomes are covered with a sticky hydrophobic substance that makes foliar deposits of ^{210}Pb or ^{210}Po stick on the leaf, whereas they might wash off from other plant leaves.

The monograph by Moroz and Parfénov (1972a) considers the intake of ^{210}Po during tobacco smoking and remarks that the urinary output of polonium is sometimes higher in smokers. However, they quote the work of Little et al. (1964), which shows no significant differences in tissue contents of polonium in smokers versus nonsmokers. But Blanchard (1967) later measured average concentrations of polonium in several tissues and found those in smokers to be slightly higher than in nonsmokers. Only the difference in concentrations in lung was statistically significant. Hill (1965) placed the difference in lung tissue at two- to threefold.

Some of the most recent work on polonium and other alpha emitters in the lung from cigarette smoking comes from New York University. It started with

Bernie Cohen's Ph.D. thesis (1979) and was taken up by N. H. Harley et al. (1979) as principal investigators, Kuschner and M. E. Wrenn as coinvestigators, and B. S. Cohen as "staff." Cohen et al. looked at the distribution of ^{210}Pb in the human lung (1978, 1979). The most recent findings are presented in the 1979 annual report. They measured ^{210}Po in cigarette smoke tar, then let it stand for decay of the polonium. The measured values for alpha activity were about 10 fCi/cigarette.

They then turned to analyses of human lung tissue using a cellulose nitrate etch film to detect the extraordinarily low values found in the bronchial tree. While there were some variations with age and some areas of higher concentration (by a factor of about one thousand), the usual concentration was a fraction of a femtocurie per square meter or about 20 fCi in the entire tracheobronchial tree. Translated to radiation dose, the average was about 1 mrad/yr, but with one or two "hot spots" at about 1 rad/yr. Significance depends much upon the real importance of such "hot spots"—a subject we will take up in chapter 9.

Since it is in the bronchi that the tumors arise, the research and the polemic had to focus on the polonium concentrations in bronchial epithelium. The results are discouragingly disparate. Not only do different investigators (by and large the ones we have already cited) differ, but their models for dose calculation are even more disparate. Moroz and Parfenov (1972a) present a full summary of the work until 1971. Their final statement sums it up well: "Thus, smoking of two packs of cigarettes a day leads to supplementary irradiation of the lungs of the smoker, equal to 0.1-100-fold absorbed dose rate in comparison with the natural background" (Moroz and Parfenov 1972a, p. 27).

An especially frustrating aspect of this wide range of possible doses is the fact that the highest approach potential biological significance, while the lowest are far too low to account for the statistics on lung-cancer incidence in smokers. Probably further research of the same nature will do little to solve the problem. Equal efforts on the basic mechanisms would be preferable, especially when we remember the growing opinion that many cancers, if not most, have multiple causation. That polonium helps to trigger a cancer already "set up" by chemical carcinogens, or vice-versa, or that there is no such effect at all, is a more interesting line of attack than more measurements of concentration. Probably for this reason, and perhaps frustration, the amount of work on polonium in tobacco and in lungs and tissues of smokers has fallen off considerably in recent years.^(a)

Part B. Thorium

I. Introduction

We are interested in thorium as a generic term for a number of different isotopes and many compounds. In the days before electric lights, fine illumination could be obtained from a gas or kerosene flame making incandescent a mantle

(a) The subject has been revived in the draft NCRP report (1986) cited earlier (footnotes, pp. 230, 231). As part of a consideration of radiation exposure to the U.S. population, it was evident that the annual effective dose equivalent to smokers far exceeded that to non-smokers, i.e., 1,660 mrem versus 365 mrem. Further, the report ascribed most of the dose to ^{210}Po - ^{210}Pb . Whether or not this is sufficient to cause lung cancer by itself is still problematical.

devised by Welsbach. This mantle was prepared from thoria but had other components also. Although its use peaked around the turn of the century, there is still much demand for such mantles from campers, the Armed Forces, etc. Thorium ores were mined and handled in quantities far larger than uranium at the time. Thorium is also used in alloys and in the making of refractories.

A nuclear fuel cycle based on the conversion of thorium to the fissionable ^{233}U has much potential and has recently stimulated a flurry of activity in the biomedical realm. Such a cycle might be brought into play if uranium reserves are depleted, because there is considerably more thorium than uranium in the earth's crust. Good summaries of its properties are given by Wrenn (1977), by Stover (1981), and in International Symposia (1963, 1965, 1968).

Biomedical research with thorium was relatively low-key during the years of World War II. It was neither a new substance nor one expected to be used in large quantities. There were no crash programs, and no single laboratory devoted more than a fraction of its efforts and resources to the subject. It was, however, an important complication in the luminous dial painter cases, as we saw in chapter 1.

It received more attention in the postwar years. This was partly to help understand better some of the luminous dial painter problems, partly through the ^{224}Ra story we reviewed in chapter 1. But it was largely through the realization that a new and large population of exposed humans was in our midst. This was the population, or rather several populations, of thousands of patients who had received the radiopaque medium "Thorotrast" in diagnostic radiology.

After a review of natural thorium and its effects and the distribution and excretion of thorium isotopes in animals and man, we will pursue a brief analysis of the Thorotrast problem and of the effects of short half-life isotopes of thorium.

II. The Setting and the Problems

When we depict the three naturally occurring series of radioisotopes as we did in the preface to these four chapters, we seldom pause to pay tribute to those who devoted whole careers to unraveling the natural decay series. Brucer (1981) describes a part of the process, including the sometimes acrimonious arguments among the radiochemists. (Hahn and Boltwood, for example, could agree only on the quality of Munich beer, which they longed for while working temporarily in the New World with Rutherford at Montreal [Brucer]). The thorium series was an especially complex one to work out, partly because the activity could range from very low and almost invariant with time to moderately high and with marked changes with time, all dependent on previous treatment of the source material.

In table 4.2, the elements of the thorium series are shown. Table 4.3 shows the uranium series. The contrast in properties of the two series is immediately apparent. All daughter products of ^{232}Th have relatively short half-lives, and the parent has a very long half-life. Thus, in contrast to the situation in the uranium series, rapid changes in activity will occur with time if work is begun with thorium separated from the daughters. In the extraction of thorium from ores or from a mixture in secular equilibrium, the ^{232}Th and ^{228}Th stay together and are separated from the radium, actinium, polonium, thoron, bismuth, thallium, and lead isotopes. But these immediately begin to reappear with a time course of gross radioactivity like that shown in figure 4.7.

TABLE 4.2. The Thorium Series

Element	Symbol	Half-life	Energy (MeV)			Percent γ Occurrence
			α	β	γ	
90 thorium	^{232}Th	1.40×10^{10} y	4.00	—	0.06	23
88 radium	^{228}Ra	6.7 y	—	0.054	—	—
89 actinium	^{228}Ac	6.13 h	—	1.11	0.90	30
90 thorium	^{228}Th	1.91 y	5.43	—	0.08	28
88 radium	^{224}Ra	3.64 d	5.68	—	0.24	5
86 radon	^{220}Rn	55 s	6.29	—	—	—
84 polonium	^{216}Po	0.16 s	6.78	—	—	—
82 lead	^{212}Pb	10.6 h	—	0.36	0.238	81
83 bismuth	^{212}Bi	60.6 m	6.05	2.20	0.04	17
84 polonium	^{212}Po	300 ns	8.78	—	—	—
81 thallium	^{208}Tl	3.1 m	—	1.79	2.62	100
82 lead	^{208}Pb		[stable]			

Source: Reset from Lapp and Andrews 1972. Reprinted with permission of Prentice-Hall, Inc., Englewood Cliffs, New Jersey, copyright 1972.

TABLE 4.3. The Uranium Series

Element	Symbol	Half-life	Energy (MeV)			Percent γ Occurrence
			α	β	γ	
92 uranium	^{238}U	4.5×10^9 y	4.2	—	0.048	23
90 thorium	^{234}Th	24.1 d	—	0.19	0.09	4
91 protoactinium	^{234}Pa	1.17 m	—	2.29	1.0	0.6
92 uranium	^{234}U	2.5×10^5 y	4.8	—	0.05	28
90 thorium	^{230}Th	8.0×10^4 y	4.8	—	0.068	24
88 radium	^{226}Ra	1602 y	4.8	—	0.186	4
86 radon	^{222}Rn	3.82 d	5.49	—	0.5	0.07
84 polonium	^{218}Po	3.05 m	6.00	—	—	—
82 lead	^{214}Pb	26.8 m	—	0.65	0.24	4
83 bismuth	^{214}Bi	19.7 m	5.5	1.5	0.61	47
84 polonium	^{214}Po	160 μs	7.7	—	0.8	0.014
82 lead	^{210}Pb	21 y	—	0.016	0.046	81
83 bismuth	^{210}Bi	5.0 d	—	1.16	—	—
84 polonium	^{210}Po	138 d	5.30	—	0.80	0.001
82 lead	^{206}Pb		[stable]			

Source: Reset from Lapp and Andrews 1972. Reprinted with permission of Prentice-Hall, Inc., Englewood Cliffs, New Jersey, copyright 1972.

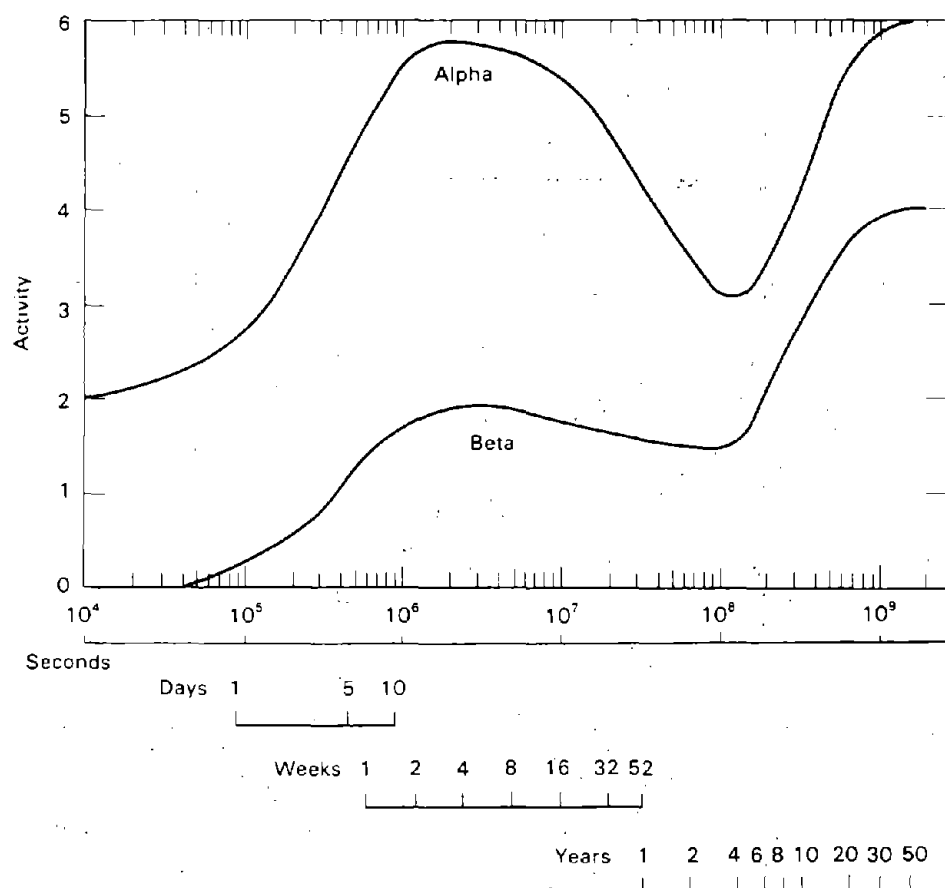


FIGURE 4.7. Radioactive “decay” of ^{232}Th plus ^{228}Th showing changes in gross activity with time. (Redrawn from F. L. Cuthbert 1958, *Thorium Production Technology*, p. 246. Reprinted with permission of Addison-Wesley Publishing Co., Inc., Menlo Park, California, copyright 1958.)

In addition, thorium isotopes occur in the other naturally occurring radioactive series. Two of them, ^{234}Th and ^{230}Th , occur in the uranium series; two others, ^{231}Th and ^{227}Th , occur in uranium minerals as members of the ^{235}U decay chain (the actinium series). Thus, if a source such as monazite sand is used, the build-up of daughter activity can be exceedingly complex, as shown in figure 4.8.

Biological studies with such a mishmash of activities coming and going are correspondingly complex and sometimes confusing. On the one hand, “natural thorium” seemed to be almost inert toxicologically. Yet, on the other hand, the maximum permissible body burdens and maximum permissible concentrations of isotopes like ^{228}Th , ^{230}Th , ^{232}Th , and the radioactivity of Th-nat are in the same range as ^{239}Pu , i.e., among the lowest on the books (ICRP 1959; NCRP 1959). In the new ICRP compilations, some of the thorium isotopes have derived air concentrations even below those for ^{239}Pu (ICRP 1979). Are both sets of facts

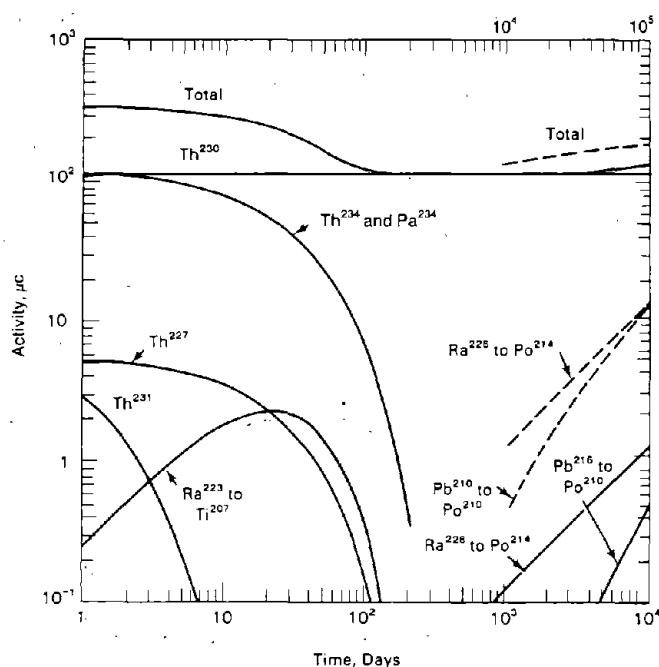


FIGURE 4.8. Daughter activity build-up from ^{234}Th , ^{231}Th , ^{230}Th , and ^{227}Th present in 1 mc of thorium obtained from Indian monazite. Broken lines are continuation of curves on scale 10^4 to 10^5 (shown at top of graph). (Redrawn from F. L. Cuthbert 1958, *Thorium Production Technology*, p. 246. Reprinted with permission of Addison-Wesley Publishing Co., Inc., Menlo Park, California, copyright 1958.)

correct, or has there been a mistake somewhere? The balance of this chapter will address this and other dilemmas posed over the years by the biomedical research with thorium and its wandering daughters.

III. Natural Thorium

A. Is There Such a Thing?

Hursh (1974) addresses this question in detail. In the strict sense and in contrast to natural uranium, there is really no specific entity with more or less constant and predictable isotopic composition present in thorium ores that we can call "natural thorium." Table 4.4, taken from the Hursh paper, shows the "natural" thorium isotopes, their specific activities, and the series in which they belong.

Thorium ores contain varying amounts of U_3O_8 , which can contribute varying amounts of ^{234}Th and ^{230}Th , and also ^{235}U , the precursor of ^{231}Th and ^{227}Th . These several components could hardly be expected to be in consistent ratio in ores

of different origins. They obviously should vary in activity with time after preparation, and there is no "natural thorium" analogous to "natural uranium."

TABLE 4.4. Thorium Isotopes of the Natural Radioactive Series

Nuclide	Half-life	Specific Activity (d/m/g)	Related Natural Series
^{228}Th	1.910 yr	1.82×10^{15}	thorium
^{232}Th	1.41×10^{10} yr	2.43×10^5	
^{230}Th	8.00×10^4 yr	4.32×10^{10}	
^{234}Th	24.10 day	5.14×10^{16}	uranium
^{227}Th	18.2 day	6.86×10^{16}	actinium
^{231}Th	25.52 hr	1.20×10^{18}	

Source: Reset from Hursh 1974. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1974.

B. Chemical Toxicology of Long-Lived Thorium

Long before the realization that "natural" thorium was not an entity of constant composition, toxicological work was done with the thorium mixtures and compounds available. The work goes back as far as 1907 and is in the literature of pharmacology and toxicology. It appeared to be a substance of very low toxicity acutely. It had the general properties of the rare earths, which meant being relatively insoluble except for a few compounds, and it was prone to deposit in the tissues and organs of the RES, i.e., liver, spleen, bone marrow, lymphatics.

During the years of most active work on uranium in the MED, a few thrusts were made to explore similarities and differences between uranium and thorium. Much of this work with "natural" thorium was done at Rochester and was reported in monthly reports. After the war and when the potentials for a thorium-based nuclear cycle drew more attention, the Rochester group looked more seriously at the chemical toxicity of natural thorium (Downs et al. 1959; Hodge and Thomas 1959; Hodge, Maynard, and Leach 1960; and others).

The earlier work (Downs et al.) explored several routes of entry and looked at weight gain, hematology, histopathology, and lethality. Maximum times ranged up to fifty to one hundred days. In a dog experiment (Hodge and Thomas 1959), a few animals were kept as long as seven years following inhalation exposure. (This experiment paralleled the long-term uranium experiment described in chapter 2 but was much smaller.)

There was virtually no specific chemical toxicity of thorium comparable to the nephrotoxic action seen with natural uranium. And despite large calculated radiation doses to the lung of dogs over a two- to seven-year period, essentially no histological evidence of radiation damage could be found. The authors muse on several possible explanations. The most likely one in their opinion is the large amount of self-absorption of the short-track alpha particles and the fact

that the deposits were very uneven and acted like point sources, i.e., large volumes of lung were not irradiated.

Since no quantitative approach was possible, the potential explanations must be considered as possible but not proven. With or without a plausible explanation, these findings were hardly indicative of an element with toxicity comparable to plutonium. Yet, the maximum permissible concentrations put it in that category: a first-class dilemma.

The same dilemma is seen also in the surveys of thorium workers. Albert et al. (1955) looked carefully at the industrial hygiene practices and the medical status of a group of eighty-four employees in a plant extracting thorium and rare earths from monazite ore and manufacturing gas mantles over a thirty-year period. Calculated radiation doses were considerably in excess of current maximum permissible exposures. But again there was no evidence of overt disease attributable to the exposure.

This, plus the animal data, led to the addition of footnotes to the permissible thorium concentrations in both the ICRP and NCRP 1959 reports. These were appended to the $(MPC)_a$ values for ^{232}Th and Th-nat as follows:

Provisional values for Th^{232} and Th-nat. Although calculations and animal experiments suggest that Th-nat, if injected intravenously, is perhaps as hazardous as Pu and indicate the values listed above, experience to date has suggested that in industrial circumstances the hazard of Th-nat is not much greater than that of U-nat. Therefore, pending further investigation the values $(MPC)_a = 3 \times 10^{-11} \mu\text{C}/\text{cm}^3$ for the 40-hour week and $(MPC)_a = 10^{-11} \mu\text{C}/\text{cm}^3$ for continuous occupational exposure (168 hr/wk) are recommended as provisional levels, permissible for exposure to inhaled Th-nat or Th^{232} . However, the values given in Table I are listed to indicate the possibility that further evidence may require lower values and to urge especially that exposure levels for these radionuclides be kept as low as is operationally possible. It may be possible to show that similar considerations apply to other inhaled long-lived thorium isotopes under conditions in which the physical characteristics of the airborne particulates are much the same as in the case of Th-nat, and where there is a large amount of airborne material serving as an effective carrier for the thorium. (ICRP 1959)

and

Provisional values for Th^{232} and Th-nat. Although calculations and animal experiments suggest that Th-nat is perhaps as hazardous as Pu and indicate the values listed above, industrial experience to date has suggested that the hazard of Th-nat is not much greater than that of U-nat. The NCRP has recognized that a certain period of time may be required for adjustment of operations to comply with new recommendations. Therefore, pending further investigation the values $(MPC)_a = 3 \times 10^{-11} \mu\text{C}/\text{cc}$ for the 40-hour week and $(MPC)_a = 10^{-11} \mu\text{C}/\text{cc}$ for continuous occupational exposure (168 hr/wk) are recommended as permissible levels. These values are essentially those that have been generally used in this country (*Federal Register* 1957). However, the values given in Table I are listed to indicate the possibility that further evidence may require lower values and to urge especially that exposure levels of Th-nat be kept as low as is operationally possible. The exception indicated here applies only to the $(MPC)_a$ values for Th-nat and Th^{232} . (NCRP 1959)

Note that the NCRP version is aimed at U.S. practices specifically.

Additional information on the nature of thorium hazards in industry is given in Albert's book (1966) and also in the Russian literature (Tarasenko 1963), but the basic information on the workers did not change the picture much except that more was said about potential hazards.

The need for a caveat in the form of a footnote to the international and national recommendations became the *raison d'être* for a conference on thorium toxicity held in Rochester, New York, January 19-20, 1960. Here the many facets of the biomedical problems with thorium were brought together, and the notion that thorium could be shelved as a toxicologically inert substance was thoroughly dispelled. The several papers given there foreshadowed most of the later toxicological work.^(a)

However, before we can go on to examine the distribution and excretion work and effects, we should pause to consider a wartime sidelight, even though it is not strictly research on the toxicology of internal emitters.

C. A World-War-II False Alarm

In chapter 6 on the fission products, we will review the concerns developed in the Allied High Command during the war in Europe that the Germans were indeed proceeding on a nuclear energy project and might even beat the Allies to producing a nuclear weapon. In Goudsmit's book, *Alsos*,^(b) which is the story of intelligence efforts to learn how much the Germans were really doing, there is a chapter involving thorium. On the liberation of Paris, it was found that a French company, under German supervision, dealing in rare chemicals had a monopoly on thorium and had moved the entire supply of thorium back to Germany. Did the Germans have work going on the thorium cycle? The mystery was further deepened when it was calculated that only a small fraction of that supply would have been needed to meet ordinary industrial needs for the next twenty years! The agents followed every lead and found the principals who were behind the movement of thorium from France to Germany. It consistently dead-ended, however, when they tried to tie it to nuclear energy matters. In fact, the people seemed to be genuinely and totally unaware of what information was being sought. And well they should have been, for it turned out that the huge chemical company concerned (the Auer Company) was planning for the postwar years and realized that the "big money" would be in cosmetics. They had a patent on *thoriated toothpaste* which they expected might compete with Bob Hope and the toothpaste he advertised with "Irium." The world's largest single stored supply of thorium ore appeared to be destined for toothpaste.^(c)

IV. Distribution and Excretion of Thorium Isotopes

A. Animal Studies

Only a fair amount of work has been done with thorium in forms where its distribution and excretion were probably governed by the fact that it was thorium rather than a colloid. There has been much more work on the colloidal

(a) In 1976, AEC's successor agency, ERDA (Energy Research and Development Administration), announced follow-up medical studies to be undertaken by ANL's Center for Human Radiobiology on employees of the Lindsay Light and Chemical Company plant now owned by Kerr-McGee Corporation.

(b) *Alsos*, Samuel A. Goudsmit, Professor of Physics, Northwestern University, Henry Schuman Inc. New York (1947).

(c) Later investigations confirmed that this was indeed all there was to it.

oxide in the form of Thorotrast, or long-lived isotopes in other forms where the behavior is strictly governed by the fact that it is in colloidal form. In some of the work, both situations prevail as a function of the amount of carrier present. This section will address this very basic problem.

While Hevesy looked briefly at the behavior of thorium, the earliest systematic work at truly tracer levels was done at U.C. Berkeley by the Hamilton group (Lanz et al. 1946; Hamilton 1947). This was under the aegis of the Metallurgical Laboratory, which we will see much more of in chapters 6 and 7. The routes were intramuscular or oral, the animals rats, and the injection about 10^{-6} mg of ^{234}Th chloride per kilogram. This experiment involved little or no complication by ingrowing daughter products since ^{234}Th decays with a twenty-four-day half-life via a short-lived beta-emitter, ^{234}Pa , to the very long-lived ^{234}U . It appeared that about 50% of the ^{234}Th deposited in skeleton. This was when the figures were put as percent (adjusted) dose per organ. Thomas (1961) recalculated the figures as fractions of the recovered dose. Since the injections were intramuscular, a large amount of the thorium remained at the injection site and was slowly released to the circulation, where, as Thomas put it, "...it follows what its chemistry demands." On this new basis, bone was still the organ with highest concentration, but it began at only 3% of the recovered dose and gradually rose to 12.2% at sixty-four days. The excretion pattern with time likewise changed qualitatively when expressed on the basis of recovered dose.

But regardless of details of the calculation, the important fact emerges that at tracer levels, and with a slow trickle into blood from the injection site, the organ of principal disposition was clearly bone, not RES tissues. This behavior looks more as an analogue of plutonium should look.

Scott, Neuman, and Bonner (1952) at Rochester gave thorium sulfate to a variety of rodents by several routes of administration. The total thorium concentration was 2.5 mg/kg, and the solution was a mixture of ^{234}Th (UX_1) and "inert" carrier, ^{232}Th . Despite an original plan to do a carrier-free experiment, this one involved carrier and illustrated the marked differences carrier could make. At the higher concentrations, the "soluble" thorium sulfate acted as a quite insoluble salt. It remained at the site of injection, was not absorbed from the gastrointestinal tract, and, after intravenous injection, went largely to liver and spleen.

Boone et al. (1958) at Los Alamos gave ^{230}Th (ionium) plus carrier ^{232}Th to rats as the citrate complex. The amounts given were 8 to 54 mg/kg, much more than in the two experiments described thus far. The distribution was different from either. There was more in bone than in the Rochester experiment, but also much more in RES organs (liver, spleen, bone marrow) and in the "remainder" tissues (skin, muscle, etc.) than in the Berkeley work. Furthermore, as the doses decreased, the fraction in bone decreased, that in the "remainder" tissues increased, and the fraction in RES tissues remained about the same. In the Los Alamos study, much of the thorium in "bone" was in marrow, while that in the University of California, Berkeley, study, at true tracer levels, was in cancellous bone. This showed that surely there were opposing factors at work, e.g., chemical properties, solubility of the salt given, and effects related to the total mass of thorium given and its propensity to form colloids.

Thomas (1961) analyzed these phenomena in detail and added the results of an experiment of his own. This experiment, done at Rochester (Thomas 1957), involved intratracheal administration of ^{230}Th (ionium) + carrier- ^{232}Th in the rat. The form was presumed to be the hydroxide, and the dose was about the same

as in the work of Scott and coworkers, 4 mg/kg. The lung acted like a reservoir much as the injection site did in the Lanz (Berkeley) experiment. A large amount was excreted in feces. But the amount in bone was only about one-tenth of that seen in the Lanz intramuscular injection experiment with tracer ^{234}Th . After an analysis of the numbers of atoms of ^{234}Th versus ^{230}Th present in the skeleton, in the original dose, and in the "reservoir" tissue if there was one, Thomas concluded that solubility at carrier thorium levels and at tracer levels differed by a factor of about five to ten when the material enters from a reservoir with a concentration difference of 10^6 .

These comparisons provided some explanations but left also some puzzling inconsistencies.

At about this time, thorium isotopes had entered the University of Utah experiment with beagle dogs, which we will review in detail in chapter 8. Thorium-228 was introduced into the long-term toxicity work because of its possible role in the radium dial painter experience (see chapter 1). It turned out that this isotope contributed inconsequentially to the toxicity of radium dial paint to the luminizers because of its poor absorption from the gut. But it was kept in the Utah experiment as an opportunity to study not only ^{228}Th but its decay series of daughters. This latter aspect was reported in detail (^{224}Ra , ^{212}Pb , and ^{212}Bi) by Stover et al. in 1965 and will be considered presently.

Let us look first at ^{228}Th itself in the dog (Stover, Atherton, and Mays 1962). At 3.5 yr after intravenous injection of tracer levels of carrier-free ^{228}Th (Rd Th), fully 80% of the retained thorium was in the skeleton. The remaining 20% was widely distributed in the soft tissues, especially liver and kidney. At the outset, liver held about 44% of the injected dose, but it fell by exponential kinetics to about 1% at 1,400 days. No problems of dose-level effects appeared, since even the highest dose was a tracer level, and the behavior did indeed look somewhat like plutonium. (Stover and coworkers compare the chemical and biochemical behavior of ^{239}Pu and ^{228}Th in detail and arrive at an interesting list of similarities and differences between these two tetravalent actinides in the beagle.)

The several symposia and annual reports from the Utah Project (see chapter 8) give retention functions for each of the elements involved in the work. It is worth noting here that the initial skeletal dose rate from ^{228}Th is higher than that from ^{239}Pu or ^{226}Ra by a factor of about four, but it falls off more rapidly so that by one hundred days the difference is a factor of two for ^{239}Pu and about three for ^{226}Ra (Stover, Atherton, and Mays 1962, p. 6).

Meanwhile, the Rochester group was planning inhalation studies with thorium. They faced the dilemma of choosing a dose that would produce effects yet would not have large carrier effects to modify the biochemistry so much that the results would have no bearing on the low levels of exposure associated with permissible occupational exposure. Thomas, Lie, and Scott (1963) decided to extend the work on distribution and excretion patterns using four routes of entry (intravenous, intramuscular, intraperitoneal, and intratracheal) and two levels of ^{234}Th with ^{232}Th carrier, viz., 5.5×10^{-6} g thorium/kg body weight and 6.4×10^{-3} g thorium/kg. The results confirmed and amplified the earlier work. At the lower tracer level, deposition in bone was significant. At the higher level, the thorium acted like a very insoluble substance and showed the properties of particles. After analyzing the work of many others in addition to their own, these workers felt quite confident that many of the puzzling contradictions of earlier studies could be explained. Indeed, thorium deserved to be considered like plutonium at low concentrations. At high concentrations, entirely different

phenomena enter, and these distribution and excretion data have no bearing on occupational exposure situations.

The fraction of thorium in "skeleton" went through a minimum at about 10^{-4} g/kg when the data from the several experiments were plotted together. The increase at lower concentrations represented deposition in cancellous bone; the increase at higher concentrations represented increasing deposition in marrow as an organ of the RES. Figure 4.9 reproduces the schematic of these phenomena taken from Thomas and coauthors. The minimum in bone deposition appears between 10^{-5} and 10^{-3} g thorium/kg injected.

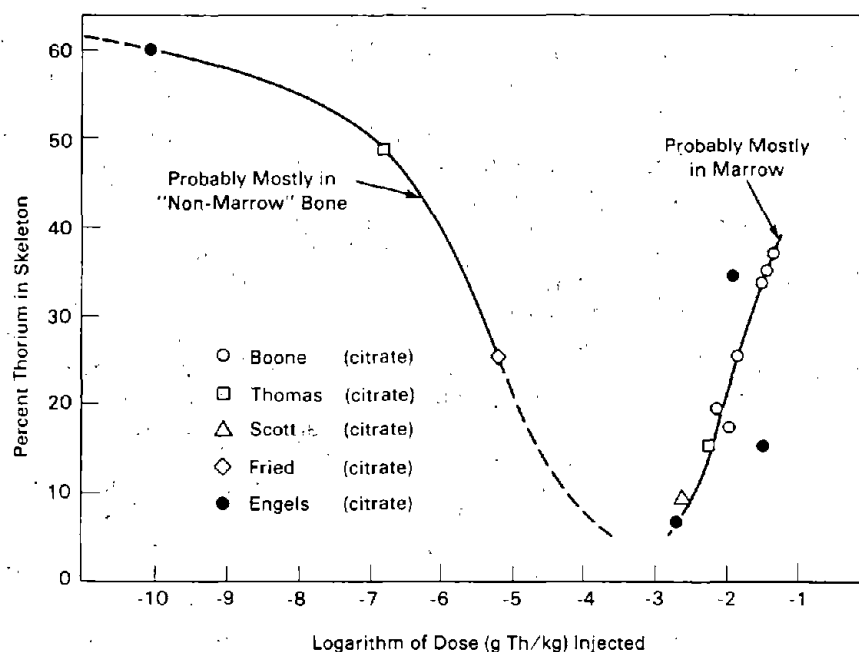


FIGURE 4.9. Percent deposition in the skeleton of rats as a function of the quantity of intravenously injected thorium. (Redrawn from Thomas, Lie, and Scott 1963. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1963.)

The first actual inhalation experiment was soon done by Boecker, Thomas, and Scott (1963). Water-soluble thorium chloride was used for the exposure aerosol. At early times after inhalation, the material behaved as if it were indeed soluble, and fairly rapid absorption from the lung took place. But this soon ceased, and very little additional absorption occurred. Any further loss from lung was almost entirely by the normal clearance mechanisms for insoluble dusts. In contrast to the work involving other routes, and despite a concentration range from 1.7×10^{-8} to 1.8×10^{-3} g thorium/kg, there was little effect of the dose size per se on the pattern of distribution and excretion. Mostly the inhaled material acted like an insoluble salt, and only about 20% of the lung burden went to bone. But neither did it go to RES tissues! It just remained in the lung

until removed and excreted in feces. Thus, the behavior after injection is not a suitable surrogate for inhalation exposure. (Fortunately, the differences would make any standards based on injection more conservative.)

Boecker (1963) then compared the behavior of inhaled ^{234}Th citrate complex with the thorium chloride used in the earlier inhalation work. This was in order to check their behavior when given by the same route. There were differences. The citrate complex was absorbed from the lungs to a considerably greater extent than was the chloride, but again only for a short period (one to two hours). After that, the two compounds disappeared from lung slowly and at the same rate. There was more in skeleton, liver, and muscle following inhalation of the citrate complex. But again the difference was all due to the initial events. It was as though both compounds were transformed to some common state shortly after deposition and behaved like a single substance thereafter.

Boecker also compared divided with single inhalation exposures. There was no real difference in distribution or excretion whether the exposures were given in two or five installments or in a single administration. The same fractions of the lung burden were absorbed on all regimens.

Unfortunately for the thorium work, Boecker left Rochester to go to the Lovelace Foundation, where he became occupied with other inhalation problems, and Thomas was occupied otherwise. Thus, the Rochester program with ^{234}Th never got extended to the area of effects. The only long-term inhalation toxicity experiment we have is the one already discussed with natural thorium. Should the thorium cycle expand or replace the uranium cycle, relative carcinogenicity to the lungs of tracer levels of thorium will need to be compared to plutonium.

The group at Case Western Reserve University looked early at concentration effects with parenterally administered thorium and came up with results (Mattis 1950) comparable to those described in the paragraphs above. Also a report from the USSR (Kendysh 1966) was in the same vein.

Let us now turn briefly to the behavior in vivo of the wandering daughters from the thorium series. Knowledge of the metabolism of each member of each series is essential for the calculation of radiation dose. Two sources have provided the bulk of the information: the Utah beagle dog experiment and whatever could be gleaned from the Thorotrast patients and other studies on man. We will look first at the beagle dog work. Stover (1981) and Stover et al. (1965) have provided the definitive information on how most of the daughters behave in the beagle. Mays, Haldin, and Van Dilla (1958) addressed the behavior of thoron produced in the ^{228}Th chain, also in the beagle. The 1965 work concentrated on blood and excreta with emphasis on ^{224}Ra , ^{212}Pb , and ^{212}Bi . It was clear that some of the daughter products indeed escaped from the beagle and, of course, these and all of their subsequent decay products did not contribute to dose. But it was concluded that such excretion does not "substantially reduce the potential α -irradiation from ^{228}Th ." Indeed, movement of ^{224}Ra , ^{212}Pb , and ^{212}Bi within the dog probably results in irradiation of many more cells than if they had decayed at the site of ^{228}Th deposition. Equations for the relative movement are provided.

The 1979 work considers the daughter concentrations in blood and excreta, but adds also the disequilibrium in tissue samples (bone, liver, spleen, kidneys). About all that can be said in the space available here is that the microdosimetry of the skeleton subjected to the ^{228}Th chain is "intriguingly complex." Even more sophisticated measuring and modeling are suggested.

Finally, as might be expected from its extremely short half-life (54.5 sec), most of the thoron (^{220}Rn) produced in the beagle body is retained rather than exhaled (Mays, Haldin, and Van Dilla 1958). Thus, there is a little loss (maximum 10%) of members of the ^{228}Th chain by formation of the inert gas. This is quite in contrast to the situation in the ^{226}Ra chain, where a significant amount of the radon is exhaled and lost from the body.

One early bit of evidence from the animal work is important. In the autoradiographic work from Berkeley, done during the war years with ^{234}Th , it was strikingly clear that its microscopic localization in bone was more like that of plutonium than of radium (Hamilton 1947). It was localized on bone surfaces near the zones of most concentrated bone growth.

In a later study, the pattern of distribution in rat liver following intravenous administration of Thorotrast was found to indicate a major cycle in the Kupffer cells and a minor cycle in the hepatic cells (Tessmer and Chang 1967). By light and electron microscopy, they were able to show a multiplicative process in the Kupffer cells; followed by limited degeneration and fibrosis. Being professional pathologists, the authors then tied the experimental findings into effects noted in human liver—a subject for the next major section of this chapter.

The actinium series ($4n + 3$) has received relatively little attention in biomedical research. Los Alamos looked at the toxicology of actinium equilibrium mixture, the individual members were included in the Berkeley work, and a comprehensive analysis of metabolism in the rat was conducted at Mound Laboratory just before it ceased biological research.

All of the essential findings can be gleaned from the summary of a published paper from Mound Laboratory by Campbell, Robajdek, and Anthony (1956), which is excerpted below:

1. Rats injected with Ac^{227} in equilibrium with its daughters (AEM) excreted about 50% of the administered Ac^{227} within three months. The remaining 50% appeared to be retained by the rats almost indefinitely.
2. Ac^{227} which was deposited in the skeleton was not excreted, whereas that deposited in the visceral organs was readily excreted.
3. Ac^{227} deposited in the skeleton remained in equilibrium with its daughters, whereas that in the soft organs was stripped of its daughters.
4. Orally administered AEM is quickly excreted in the feces. Less than 0.1% is retained by the rat.
5. Normal skin is an effective barrier to AEM. Abraded skin allows some passage of Ac^{227} and its daughters into the rat.
6. No appreciable amount of Ac^{227} or its daughters is transferred across the placenta of injected females to their young.
7. Radioactive substances were excreted in the milk of lactating rats injected with AEM. The radioelements responsible for their activity were Ra^{223} (80 to 90%) and Th^{227} . No Ac^{227} was found.

Obviously, the distribution and excretion work with thorium in animals showed the many facets of its behavior and the complexities of trying to arrive at reliable calculations of radiation dose. On balance, the work made the pegging of the $(\text{MPC})_a$ at low values seem much less questionable than when we only had data from natural thorium.

B. Distribution and Excretion of Thorium Isotopes in Man

The characterization of the metabolic behavior of the several thorium isotopes and their progeny in animals was a considerable achievement. But there was the usual question of the extent to which the animal data could be applied to man. Despite the much greater difficulties occasioned by lack of tissue samples and of controlled experimental conditions, several quite satisfactory investigations have been conducted in man.

1. Thorotrast

The principal source has been, of course, the patients who received Thorotrast in the period 1930 to 1950. These have a feature seldom present in retrospective studies on man, i.e., the administered dose was reasonably well known. This was because the injections of Thorotrast as a radiopaque medium were fairly standardized around the world. They have the disadvantage of the passage of frequently long time intervals between injection and study and the frequent presence of illness in the patients. Fortunately, the first disadvantage is almost nullified by the tenacious retention of Thorotrast. We will examine the work of two laboratories in some detail and only refer to the others.

A landmark study was done jointly by John Hursh and associates at the University of Rochester and William B. Looney and associates at the Radioisotope Laboratory of the U.S. Naval Hospital, Bethesda, Maryland (Hursh et al. 1957). This built upon still earlier autoradiographic work of Rotblat and Ward (1953) and measurements by Rundo (1955) and Stenstrom (1941). Stenstrom used both human subjects and rabbits. Hursh et al. used a spectrographic procedure for ^{232}Th much like that used for measuring natural uranium and radioactivity measurements for the other isotopes. They measured tissue distribution and excretion of ^{232}Th and ^{228}Th , ^{224}Ra and ^{228}Ra . They also used an external gamma counting technique to correlate with the excretion measurements and employed two human subjects who had received Thorotrast not too long before the measurements were made. These provided data on excreta for 17 to 236 days, respectively. There were autopsy tissues from four Thorotrast patients including the two just mentioned. The excretion measurements were updated by Hursh at a symposium of the New York Academy of Sciences (Hursh 1967).

The findings paralleled those we have already seen in the animal work, i.e., very slow excretion, long retention (biological half-life over four hundred years), slightly more rapid excretion of ^{228}Ra , and considerably more rapid excretion of ^{224}Ra . The calculated tissue doses from deposited Thorotrast were highest in liver and spleen, a factor of ten lower in bone marrow, and still lower in lung. There was no question but the distribution of dose from deposited Thorotrast and its daughters was quite different from that of radium and its progeny. The dose to skeleton was low and mostly to the bone marrow.

An unexpected phenomenon was the behavior of ^{224}Ra . At early times, it behaved like ^{226}Ra , i.e., like a freely diffusible ion. But at later times, much less was excreted than expected, and the ^{224}Ra acted as though it were entrapped in the large colloidal aggregates of Thorotrast.

A second relatively major effort came from the Radiological Physics Division at Argonne National Laboratory and the Department of Research and Isotopes of the International Atomic Energy Agency in Vienna (cf. the work of R. M. Parr and R. A. Dudley).

The early reports were ANL reports where Marinelli, Miller, Lucas, Parr, and colleagues described the translocation of thorium daughters to bone (ANL

Report-5689, 1957; ANL Report-5967, 1958; ANL Report-6398, 1961). This was followed by a very complete analysis by Parr, Lucas, and Griem in the June 1969 annual report (ANL-7615). Some of this work was published in the proceedings of the symposium held by the New York Academy of Sciences^(a) (Parr 1967; May, Marinelli, and Corcoran 1967). There was a complete recapitulation of the dosimetry by Dudley (1967).

The ferreting out of the activities of seven nuclides in vivo in six human patients and nine experimental animals rivaled in scientific detective work the original depiction of the thorium series. The nanocuries per organ and the alpha-ray dose were summarized by Parr and coworkers (1969) and by Dudley. These are shown in section B 3 below.

Similar results have been obtained in many other laboratories in the United States and abroad. Special mention should be made of the study by Cohn, Gušmano, and Robertson (1967) at Brookhaven National Laboratory, since they were able to deduce doses to liver and spleen entirely by whole-body counting techniques. Maletskos et al. (1969) at the Massachusetts Institute of Technology (MIT) injected soluble ^{234}Th in five elderly subjects and gave oral doses to six similar subjects. They confirmed the very small absorption of thorium from the gastrointestinal tract and that the main route of excretion was feces. Many of the epidemiologic studies abroad involved also measurements of dose in vivo. The work came from Denmark, West Germany, Austria, Czechoslovakia, and Japan, among others, as indicated in the table of contents of symposia (e.g., Lake Geneva, Wisconsin, [Rundo, Failla, and Schlenker 1983] and IAEA symposia), as well as many papers in the journal, *Biophysik*, and in *Health Physics*.

At the microscopic level, the problems raised by the autoradiographic work in animals were pursued in the human material. Jee et al. (1967, 1969) at Utah found the activity of ^{228}Th to be much higher in spongy bone than in compact bone from two Thorotrast patients and a large dog. They reconstructed the dose to the entire skeleton as well as the areas examined by careful track counting and some brave extrapolations. They had only one sample of bone from one patient and a few samples from the other. Nevertheless, the calculated total activity in skeleton (1% to 2% of injected dose on the basis of ^{232}Th) was comparable to that found by the more direct means of whole-body and sample radioactivity counting. Probably the most important contribution of work such as this, and there is much more than we can quote here, relates to microdistribution. The ^{232}Th and daughters were diffusely, but unevenly, distributed with occasional "hot spots." Macrophages loaded with alpha activity were frequently the source of the hot spots, and they were seen sometimes adhering to the endosteum, especially when the burden time had been long. Ratios of hot spot to diffuse (average) distributions were over ten for cortical bone, much less for spongy bone.

There is no doubt that quantitative autoradiography has a place in internal emitter research. But one wishes in the case of the Thorotrast problems that it were as good for soft tissues as for bone. Qualitatively, autoradiographs of tissues like liver and spleen show the presence of many, sometimes very large, aggregates whose significance depends upon the amount of self absorption,

(a) Some of the same work and studies abroad were presented in a symposium in Vienna in 1965; which we will discuss in the next section.

their location, and the true importance of microdose distributions. But only recently have the techniques been as good for soft tissue as for bone.

2. Other Sources of Data on Man

An important compilation on thorium in human tissues from sources other than Thorotrast is found in a Nuclear Regulatory Commission report prepared by the New York University (NYU) group with help from Geno Saccomanno in Grand Junction, Colorado (Wrenn et al. 1981). The principal findings in this report were summarized at the Lake Geneva Symposium on Radium and the Actinides in 1981 (Ibrahim et al. 1983).^(a) For these, twenty-two sets of tissues were obtained at autopsy from persons residing in Grand Junction, Colorado, or Washington, D.C. There was no known occupational or unusual environmental exposure to thorium in either population, except for one uranium miner and one hard-rock miner. They measured ^{228}Th , ^{230}Th , and ^{232}Th in each case.

Consistent with thorium's reputation for complexity, the results were different for different isomers and between the two locations. This can be seen in table 4.5, taken from the published paper (Ibrahim et al. 1983).

The work suggested that nonmining residents living in the vicinity of uranium mill-tailings (Grand Junction) do not have elevated ^{230}Th concentrations in their lungs compared to residents of Washington, D.C., but the concentration in bone was "just significantly higher" in the Grand Junction residents.^(b)

TABLE 4.5. Order of Concentrations of Three Thorium Isotopes^a in Autopsy Tissues from Two Small Populations

Isotope	Location	Order of Decreasing Concentration
^{228}Th	Grand Junction	Lymph nodes > bone > lung > kidney > liver
	Washington, DC	Lymph nodes > bone > lung > kidney > liver
^{230}Th	Grand Junction	Lymph nodes > bone > lung > kidney > liver
	Washington, DC	Lymph nodes > lung > bone > liver > kidney
^{232}Th	Grand Junction	Lymph nodes > lung > bone > kidney > liver
	Washington, DC	Lymph nodes > lung > bone > liver > kidney

Source: Reset from Ibrahim et al. 1983. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1983.

Wrenn, Singh, and Saccomanno (1983) also presented radiochemical analyses for uranium and thorium isotopes in the lungs of seven uranium miners obtained at autopsy. The combined radiation dose rate due to the three long-lived radionuclides, ^{238}U , ^{234}U , and ^{230}Th , was calculated to be from 2.5 to 14.2 mrad/yr, mean 9.6 mrad/yr. Only a portion of this dose would come from the thorium.

(a) Some of the NYU investigators (Wrenn and Singh) had by the time of publication moved to the University of Utah. The conference was held in 1981.

(b) There were also measurements on Grand Junction soil, but this did not explain the tissue results.

Tissue contents of thorium workers have been reported but do not contribute much to an analysis of dose. Further work is under way.

One case of an accidental puncture wound with ^{227}Th occurred at ANL and was reported in a publication by Gustafson, Marinelli, and Hathaway (1957). There was a fairly complete study of elimination and retention of both the ^{227}Th and its decay product, ^{223}Ra . The case is complicated by the fact that the injection site was excised surgically, and there was treatment with a chelating agent. Nevertheless, and discounting these complications, it appears that the ^{227}Th is more mobile. It cannot be determined whether or not this extra mobility is a property of the isotope or of the low concentrations involved, or both. The animal work would clearly favor the second explanation.

3. Recapitulation

In view of the tortuosities of the thorium series and the many points for useful comparison with radium and plutonium, recap of the information on distribution and excretion might be beneficial.

A clear summary is given by Mays et al. in the Utah symposium published in 1969. This bears on the behavior of carrier-free ^{232}Th deposits in the beagle and relations to plutonium. The summary follows:

About 70% of the carrier-free ^{228}Th deposits in the Beagle skeleton when injected intravenously in citrate solution. Microscopically the deposition on bone surfaces appears similar to that of ^{239}Pu . Both ^{228}Th and ^{239}Pu are retained tenaciously in bone. However, they differ in radiation characteristics. Whereas the long 24,000 year physical half-period of ^{239}Pu gives a fairly constant skeletal dose-rate throughout life (see Figure 1), and 1.9 year physical half-period of ^{228}Th causes over half of the life-span dose to be delivered during the first 2 years, by 10 years virtually all of the injected ^{228}Th has decayed away. The soft-tissue range of ^{239}Pu α -particles is 35 microns, whereas it varies from 38 to 82 microns for ^{228}Th and its daughters. Therefore, the α -particles from the ^{228}Th series in bone reach out farther into the marrow.

The short-lived daughters of ^{228}Th create special complications. When ^{228}Th decays to ^{224}Ra , a fraction of this radium isotope reaches the circulation. Part is excreted, and part redeposits such that in bone the total ^{224}Ra activity is about 90% of that of ^{228}Th . The highest skeletal concentration of the redepositing ^{224}Ra is in the active sites of new bone formation. This occurs continually, so that all new bone formed after ^{228}Th injection has an enhanced probability of being irradiated during its critical time of formation. The next daughter ^{220}Rn (thoron) is a noble gas. Its short 56 second half-period prevents significant loss from the skeleton, but may allow some diffusion into fat-containing cells in the marrow. Thoron is about 15 times more soluble in fat than in blood. A small amount of ^{212}Pb tags blood cells and thus delivers low doses to all body tissues. The combined escape of ^{224}Ra , ^{220}Rn (thoron) and ^{212}Pb is such that in bone the ^{212}Pb activity is about 86% that of ^{228}Th . Some ^{211}Bi (the next daughter) is taken up from the blood by the kidney. In the liver the activity of ^{212}Pb is slightly higher than that of ^{224}Ra , which is about 30% higher than that of ^{228}Th .

The soft-tissue depositions of ^{239}Pu and ^{228}Th are quite different, despite their similar-appearing deposition in bone. A year after ^{239}Pu injection, about 20 to 30% of the injected ^{239}Pu is retained in the liver, but the retention is only about 0.2% in the kidneys and 2 in all the other tissues. In contrast, the 1-year biological retention of ^{228}Th is about 3% in the liver, 1 to 2% in the kidneys and 8% in the remaining soft tissues. The dose to the kidneys from ^{228}Th and its daughters is about 10 to 30% of that to the skeleton. A characteristic and severe damage to the kidney termed

"radiation nephritis" has been observed in high-level ^{228}Th dogs, as well as significantly increased values of inorganic phosphorus in the serum.
(Quoted with slight modification from Mays et al. 1969)

Some additional thoughts for the comparison of thorium and plutonium are emphasized in Betsy Stover's paper at the 1979 Utah conference already cited. Thorium exists only as the tetravalent ion in aqueous solution, whereas plutonium has several valence states, four of them moderately stable. Toxicological work has arbitrarily been arranged to have the plutonium in the tetravalent state. But it was sometimes in other states or transformed to them.

The nearest we can come to a similar recapitulation for the metabolism of thorium-series isotopes from Thorotrast is to reproduce the calculated organ contents in the steady state and alpha-ray dose from the last and most complete of the ANL studies (Parr, Lucas, and Griem 1969). These are shown in tables 4.6 and 4.7. Included in table 4.7 are these authors' comparisons of estimated organ dose rates among the several studies.

TABLE 4.6. Thorium-Series Activities and Mean Dose Rates in Various Organs (50 ML Thorotrast Injected Intravascularly)

Organ	Wet weight, g	Nanocuries in Organ at Steady State							α -ray Dose from all Isotopes, Rad/year
		^{232}Th	^{228}Ra	^{228}Th	^{224}Ra	^{220}Em and ^{214}Po	^{212}Pb	^{212}Bi	
Whole Body	70,000	1,250	625	625	580	530	525	525	
Liver	1,700	860	430	390	270	215	135	90	71
Spleen	150	210	105	95	67	54	35	25	168
Red bone marrow	1,500	100	25	30	20	40	40	40	18
Lungs	1,000	10	5	3	3	30	30	30	13
Blood	5,400	0	0	0	3	100	55	55	6
Kidneys	300	1.3	0.3	0.6	0.5	0.4	2	4	3
Skeleton (marrow-free)	7,000	15	25	30	50	48	45	45	3

Source: Modified from Parr, Lucas, and Griem 1969.

It is quite obvious how much higher the dose is to soft tissue and how much lower it is, relatively, to marrow-free skeleton when the thorium-series isotopes are produced in vivo from colloidal deposits of thorium dioxide. This may seem a rather obvious conclusion, hardly worthy of the intense effort necessary. But note that it is quantitative and far beyond a simple declaration of facts. It is essential for dose calculations.

TABLE 4.7. Summary of Estimated Dose Rates to Organs of Thorotrast Patients

Author	Year	Mean Organ Dose Rate ≥ 20 Years After 50 ml Thorotrast Intravascularly, rad/year(a)						
		Liver	Spleen	Red Bone Marrow	Kidney	Lung	Skeleton	Blood
Parr et al.	1967	71	168	18	3	13	3	6
Hursh	1965					4-9		
Muth	1965					4-7		
Kaul	1964,65	65	145	30			2	
Rundo	1958	68	178	14-61		5		1
Hursh et al.	1957	78	78	8		3		
Reynolds et al.	1957						4-9	

(a) Dose rates reported by the different authors in most cases do not refer to 50 ml of Thorotrast. The values quoted here have been normalized on the assumption of proportionality between dose rates and volume of administered Thorotrast, though this is not strictly true because of differences in self-absorption of the radiation.

Source: Modified from Parr, Lucas, and Griem 1969.

V. Effects of Thorium-Series Isotopes

A. The Thorotrast Saga

The thousands of patients who received Thorotrast in the practice of radiology over two decades constitute the fourth major human population exposed significantly to the biological action of alpha particles produced by radioactive decay of the heavy elements. The others are, of course: (1) the radium dial painters, chemists, and patients discussed in chapter 1; (2) the German population that received the short-lived ^{224}Ra as a therapeutic nostrum, also described in chapter 1; and (3) the uranium miners exposed to radon and its daughters, discussed in chapter 3. We could add the MED uranium workers, but they are essentially a silent group thus far except for chemical toxicity (see chapter 2). The plutonium workers of World War II are a sixth potential population, but as we will see in chapters 8 and 16, they too have been silent to date, even though study has been extensive. Thus, there are four populations that are providing definite evidence of effects out of a total of six.

Some concerns were expressed for long-term effects of Thorotrast relatively soon after its use began in earnest. Cancer in animals was reported as early as 1933 by Oberling and Guérin and in 1936 and 1938 by Selbie, who confirmed the French work. Andervont and Shimkin (1940), at the National Cancer Institute, extended the work with particular concern for lung tumors. They found

find subcutaneous sarcomas and one hemangioma. Selbie declared in his *Lancet* paper: "Thorotrast should never be introduced into the human body because of the danger of inducing tumor formation."

Other authors predicted that cancer would appear in man on a priori grounds, i.e., the long retention time and the fact that the radiation was from alpha particles.

These warnings did not stop the use of Thorotrast, although it did begin to decline. The biggest jolt came when the American Medical Association Council on Pharmacy and Chemistry removed it from their approved list. But this was just before World War II, and either the word did not spread or radiologists were too preoccupied to find substitute radiopaque media. It appears that its use declined considerably during the war but did not actually cease until about 1950.

In the early years, many who questioned the use of Thorotrast were told how low its radioactivity was compared to that of ^{226}Ra , which was then the only other radioactive material in general use in medicine and industry, and that the thorium in Thorotrast could not possibly cause radiation damage. Those making such statements neglected the large differences in mobility between radium and thorium. Also, they neglected the fact that ^{232}Th is the parent of a chain of radioactive materials of very different characteristics from the daughter products of ^{226}Ra .

The end of World War II brought the opportunity to focus down on Thorotrast and to demonstrate its effects. As it became apparent that very sizeable populations carrying Thorotrast existed in several parts of the world, a series of conferences and symposia were convened, and the dimensions of the problem gradually unfolded. The story is still far from complete in terms of the desired dose-response relationships. But the fact emerged that cancer of soft tissues, particularly liver, was a serious and not infrequent long-term effect. Leukemia incidence was also increased, but not so markedly. Bone cancer incidence was not materially increased.

The major studies are distributed throughout the world, and, despite the general need for this book to emphasize U.S. contributions, we will consider the picture in many countries.

Three large European surveys are in progress. The oldest is in Denmark, under the career-long tutelage of Mogens Faber at the Finsen Laboratory in Copenhagen. The most recently organized survey is the West German project, with which we associate, among others, the names Muth and Kaul. Finally, there is a fairly homogeneous population in Portugal, with which we associate especially the name da Silva Horta.

A Japanese population and study was reported by Tsukamoto (National Institute of Radiological Sciences) and is being carried forward by his colleagues. There is also some follow-up work in England appearing from the Institute of Cancer Research at Sutton, Surrey.

Groups in the United States interested in Thorotrast effects are somewhat scattered. Norman Telles and others worked with the Massachusetts General Hospital, MIT, and Harvard researchers including Shields Warren, and U.S. Public Health Service Representatives. Looney (1960) contributed some patient experience from the U.S. National Naval Hospital. This was used in part in the Rochester dosimetry work already discussed (Hursh et al. 1957). The Argonne National Laboratory group, likewise concentrating on dosimetry, got patient records and samples from the Mayo Clinic, among others. The Salt Lake City

group, which got involved in dosimetric research primarily because of Mays's interest in ^{224}Ra , has been involved in several reviews of the entire effort.

Fortunately, these efforts have been very well documented in a series of symposia and associated monographs, and we can bypass the developmental stages and look at the status as of approximately the midseventies.

First, the symposia and monographs are given in approximate chronological order:

1. The Dosimetry and Toxicity of Thorotrast. Joint IAEA-WHO meeting, Vienna, 4-7 October 1965. Published as IAEA Report 106 in 1968.
2. Distribution, Retention and Late Effects of Thorium Dioxide. A meeting at the New York Academy of Sciences in 1965, published as Vol. 145, Art. 3, Pages 523-858 of *Annals of the New York Academy of Sciences* dated December 11, 1967.
3. International Symposium on Biological Effects of ^{224}Ra and Thorotrast. Held at Alta, Utah, 21-23, July 1974. Published as Vol. 35, No. 1 of *Health Physics*, July 1978.
4. A symposium at Copenhagen with a series of papers, which may or may not comprise the entire proceedings, published in *Environmental Research*, Vol. 18, 1979.

Since the last meeting may or may not be generally available, a selection of titles from the pertinent issue of *Environmental Research* is given herewith:

1. Thorotrast Dosimetric Study in Japan. Y. Kato, T. Mori, and T. Kumatori, National Institute of Radiological Sciences, Chiba, and Kanagawa Prefectural Junior College of Nursing and Medical Technology, Yokohama. *Environmental Research* 18: 32-36 (1979).
2. Twenty-Eight Years of Continuous Follow-up of Patients Injected with Thorotrast for Cerebral Angiography. Mogens Faber, The Finsen Laboratory, The Finsen Institute, Copenhagen. *Environmental Research* 18: 37-43 (1979).
3. Epidemiological Follow-Up Study of Japanese Thorotrast Cases. T. Mori, T. Maruyama, Kanagawa Prefectural College of Nursing and Medical Technology, Yokohama; Y. Kato, and S. Takahashi, National Institute of Radiological Sciences, Chiba; and Hamamatsu University School of Medicine, Hamamatsu. *Environmental Research* 18: 44-54 (1979).
4. Prospective Epidemiological Study of Thorotrast-Exposed Patients in Portugal. Luiz Cayolla da Motta, National School of Public Health, Secretariat of State for Health, Lisbon, Portugal; Jorge da Silva Horta, Institute of Pathology, Faculty of Medicine, Lisbon; and Maria Helena Tavares, Hospital of Santa Maria, Lisbon. *Environmental Research* 18: 152-172 (1979).
5. Statistical Analysis of Japanese Thorotrast-Administered Autopsy Cases. T. Mori, Y. Kato, T. Shimamine, and S. Watanabe, Kanagawa Prefectural College of Nursing and Medical Technology, Yokohama; National Institute of Radiological Sciences, Chiba; University of Tokyo School of Medicine, Tokyo; and University of Hiroshima School of Medicine, Hiroshima. *Environmental Research* 18: 231-244 (1979).

In addition, an earlier description of the Portuguese study was presented in Volume 8 of the same journal:

Thorium Dioxide Effects in Man: Epidemiological, Clinical, and Pathological Studies (Experience in Portugal). J. da Silva Horta, L. Cayolla da Motta, and

Maria Helena Tavares, Department of Pathology, Faculty of Medicine, Lisbon. *Environmental Research* 8: 131-159 (1974).

Many individual reports were given as parts of IAEA symposia on more general subjects, at the Atoms for Peace Conferences, and festschrift events. A good summary of the findings to 1978 is shown in table 4.8, modified from Mole's paper (1978).

TABLE 4.8. Tissue Dose and Tumour Excess in Thorotrast Patients Compared with Risks from Other Examples of High-LET Radiation

Tissue of Origin or Type of Tumour	Average Tissue Dose 30 yr After 25 ml. of Thorotrast*	Excess Tumours in 4000 Subjects	Induction per rad per 10 ⁶ Persons After 30 yr	
			Thorotrast α -particles	Other Sources of High LET Radiation
Liver	750 rad	245	80	88: Faber for Thorotrast.
Lung (bronchi)	60-620	none definite		300: from BEIR I Table p. 150 giving 1 case 10 ⁻⁶ per year per rem for miners exposed to ²²² Rn with RBE equal to 10 for α -particles.
Bone endosteum	480 (all sources) 210 (translocated)	2-6	1-3 2-7	10: Speiss and Mays for ²²⁴ Ra in adults and an endosteal/av. skel. dose ratio of 9.
Leukaemia- (marrow)	270	44	40	200: Deduced by Mole for neutron dependent leukaemia.
Multiple myeloma (marrow)	270	5	5	
Lymphoid tissue malignancy	unknown	10	?	

*Doses from Kaul and Noffz, or Mays; the same symposium; pp. 113-121 and 123-125.

Source: Modified from Mole's summary paper (Mole 1978) at the Alta, Utah, symposium. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1978.

The interest abroad in the Thorotrast story has gradually kindled interest in the United States, primarily in the form of helping with dosimetry and being sure the data were considered by national organizations, such as the National Academy of Sciences and the NCRP. No organized epidemiologic survey has yet been put together to study the U.S. population of Thorotrast patients.^(a) The coordinated in-depth epidemiology remains primarily in the European centers and Japan.

(a) There is no easy explanation for this hiatus. Perhaps the more centralized cohesive populations in Europe are better suited. Perhaps a higher percentage received Thorotrast.

The production of liver cancer in the Thorotrast patients struck a responsive chord in the Utah group, since they were beginning to see liver cancer in the long-term beagle dogs that had received actinide elements. This has led Mays, in particular, to a deep interest in the subject and some calculations of risk. His summaries of the Thorotrast findings (Mays 1979) are pertinent to this discussion. In table 4.9, we see his summary of the European population size and liver cancer incidence. In table 4.10, we see a breakdown of the liver tumors by country and by type of cancer.

TABLE 4.9. Thorotrast Patients Surviving at Least 10 Years After Intravascular Injection

Country and Year of Last Follow Up	Cases of Liver Cancer	Traced Patients Surviving at Least 10 Years	Person-yr at Risk from 10 yr Post Injection to Death or Last Contact
Germany, 1977	176	1,733	28,424
Denmark, 1977	50	646	12,274
Portugal, 1974	75	667 ^a	12,673 ^a
Total	301	3,046	53,371

^a The fraction of the Portuguese patients surviving at least 10 years, and their average time to death or last contact, was considered similar to that documented for the Danish patients. In both countries, suspected brain diseases were the main reason for the intravascular injection of Thorotrast (80% in Portugal and nearly 100% in Denmark).

Source: Modified from Mays 1979.

TABLE 4.10. Liver Cancers in Thorotrast Patients (at Latest Detailed Tumor Classification)

Types of Liver Cancer	Germany as of 1975	Denmark as of 1977	Portugal as of 1974	Japan as of 1975	Total
Angiosarcomas ^a	37	20	19	20	96
Bile-duct carcinomas	48	15	11	57	131
Hepatic-cell carcinomas	21	15	2	10	48
"Liver" carcinomas ^b	20	0	0	0	20
Unspecified ^c	14	0	43	6	63
Total					358

^a In the general population the most frequent types of primary liver cancer are hepatic-cell carcinomas and bile-duct carcinomas. Angiosarcomas are extremely rare, except in persons exposed to Thorotrast, arsenic, or vinyl chloride.

^b Either bile-duct carcinoma or hepatic-cell carcinoma.

^c Fatal, but not classified histologically, except for one case of reticulosarcoma in the Portuguese series.

Source: Modified from Mays 1979.

Using 25 rad/yr as the dose from 26 ml of Thorotrast, Mays gets 1,334,275 person-rad for the data in table 4.9. After some further calculations and debate on what fraction of the total radiation dose is wasted (i.e., occurs after the cancer has been initiated), Mays calculates a rounded risk figure of 300 liver cancers/ 10^6 person-rad of alpha radiation. It will be noted that this is considerably higher than Mole's slightly earlier estimate (table 4.8). This and other discrepancies require further work for adjudication.

Despite what appear to be large populations and long observation times, Mogens Faber considers that the work must continue to a population size of 10,000 to 20,000 and an observation period of at least twenty-five years (Faber 1968). To accomplish this may require a coordinated international effort.

The primary lesson to be learned from the Thorotrast cases is not to forget that radionuclides that seek soft tissue can be of as much concern as the bone seekers if they are markedly insoluble, have very long residence times, and especially if they have a family of wandering daughters.

A nagging complication in the Thorotrast work is the question of chemical toxicity, particularly in the liver. Thorotrast is not pure thorium dioxide. It contains some chemical additives to help preserve the colloidal state, etc. There is no series of cases with pure colloidal thorium dioxide of sufficient magnitude to act as a control for the Thorotrast observations. Some investigators are not even convinced that the toxicological research with natural thorium can be applied to long-term exposures, despite the indications that it is almost inert chemically. Much needed is a carefully designed experiment using some other radionuclide with radiation properties comparable to those of the thorium isotopes in Thorotrast but without the additives and other complexities of Thorotrast. Such an experiment is under way, using animals, at the University of Utah with a surrogate for thorium (americium). Preliminary results indicate no effect that cannot be accounted for by the radiation dose.

B. The Effects at Tracer Levels and of the Shorter-Lived Isotopes

The effects story with noncolloidal preparations of thorium isotopes, i.e., relatively low concentrations and the shorter-lived isotopes, has been largely an American enterprise. The effects follow what might be expected from the metabolic behavior described in section IV. The major effect, except at early times, is the *induction of bone cancer*. The information is largely from animal experiments.

1. The Utah Beagle Dogs

The major portion of our information on effects of the shorter-lived thorium isotopes comes from the long-term experiment with beagle dogs at the University of Utah to be described in detail in chapter 8. Thorium-228 was introduced, as discussed earlier, because of its possible role in the illnesses of the radium dial painters. All levels were sufficiently low to avoid colloid formation in substantial amount. The injection route was intravenous.

Hematological effects at the "3 level" of ^{228}Th ($0.3 \mu\text{Ci/kg}$) were comparable to those of ^{226}Ra , ^{239}Pu , ^{228}Ra , and ^{90}Sr at the "5 level," i.e., $10.35 \mu\text{Ci/kg}$, $2.88 \mu\text{Ci/kg}$, $8.47 \mu\text{Ci/kg}$, and $97.48 \mu\text{Ci/kg}$, respectively (Dougherty and Rosenblatt 1971), an indication of high effectiveness.

As the bone-tumor incidence unfolded, there was no doubt the ^{228}Th was very effective indeed. As seen in the relative biological effectiveness plot given in

chapter 8 (figure 8.8B), ^{228}Th topped the list in producing death from osteogenic sarcoma in the beagles. In the summary (Mays et al. 1969) quoted in part at the end of section IV, we see some of the possible reasons for this special effectiveness. Thorium-228 had an effectiveness relative to radium of about eight at the "1.5 and 1" levels, as high as nineteen at the "2" level, and about the same as ^{239}Pu , i.e., about six, at the lower levels. (a)

By the time of the twentieth anniversary symposium of the Utah project, they felt they had enough data to plot a dose-response relationship and to estimate risks (figure 4.10). This was published in an annual report in March 1970 and by Mays and Lloyd (1972) in the symposium proceedings. The summary data are shown in table 4.11. Stover (1979) presented an update of the figures at the Snowbird, Utah, symposium (table 4.12). This gives calculated total radiation dose to the skeleton in rad, an updating of the occurrence of osteosarcoma, and the percentage life-span shortening. These results from Utah bring us full circle back to the maximum permissible concentrations for Th-nat and ^{232}Th discussed in section III B. Certainly the shorter-lived ^{228}Th is a very effective carcinogenic agent in bone. Conservatism dictates consideration of exposure limits comparable to plutonium for the progenitor nuclides, ^{232}Th or Th-nat, when exposure is prolonged.

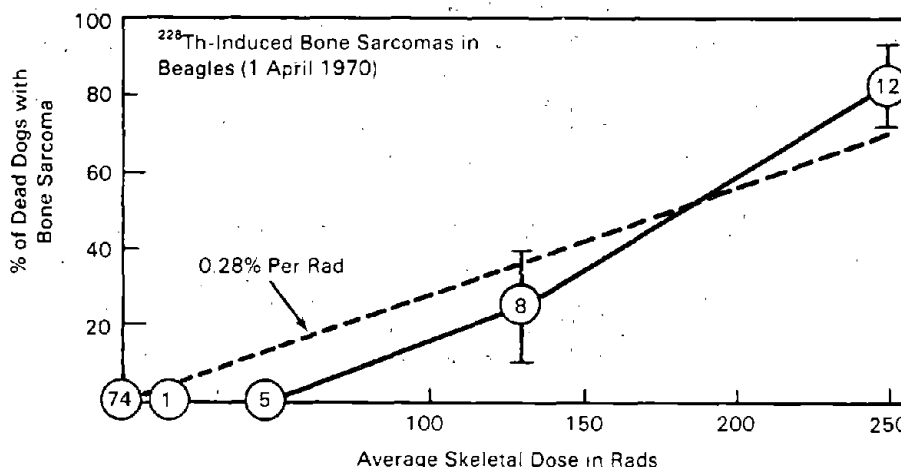


FIGURE 4.10. Thorium-228 dose-response in beagles injected intravenously with monomeric ^{228}Th in citrate solution. The indicated linear relationship predicts 0.7 sarcoma cases among the six dogs that have died without bone tumors at the 16- and 47-rad levels. (Redrawn from Mays and Lloyd 1972. Reprinted with permission of J. W. Press, Salt Lake City, Utah, copyright 1972.)

(a) These "levels" are given in detail in table 8.4, chapter 8. The ^{228}Th levels are shown in table 4.11.

TABLE 4.11. Thorium-228-Injected Beagles (1 April 1970)

Inj. Level	$\mu\text{Ci/kg}$ Inj.	Inj. Dogs*	Dead Dogs	Sar. Dogs	Incidence- (Sar./Dead)	Bone Sarcoma Dogs	
						Years from Inj. to Death	Rads 1 yr. Before Death
5	2.70	2	2	0	0	—	—
4	0.858	4	4	2	50	2.02	2870
3	0.290	12	12	12	100	2.38	1150
2	0.0919	13	13	12	92	3.26	516
1.5	0.0302	13	12	10	83	6.52	249
1	0.0152	12	8	2	25	8.75	130
0.5	0.00518	12	5	0	0	—	47†
0.2	0.00171	13	1	0	0	—	16†
0	0	13	6	0	0	—	0†

* Dogs injected 1954-1963.

† For levels without bone sarcoma, rads at 10 years.

Source: Reset from Mays and Lloyd 1972. (Reprinted with permission of J. W. Press, Salt Lake City, Utah, copyright 1972.)

TABLE 4.12. Life-Shortening and Occurrence of Osteosarcoma in Beagles Injected with ^{228}Th

Injected Dose ($\mu\text{Ci/kg}$)	Number of Beagles	Dose to Skeleton (rad)	Life-Shortening (%)	Occurrence of Osteosarcoma (%)
2.70	2	5330	88	0
0.858	4	6100 (± 580)	75	50
0.290	12	2220 (± 283)	72	100
0.0919	12	839 (± 83)	64	100
0.0302	12	348 (± 25)	39	92
0.0152	12	180 (± 11)	16	42
0.0052	12	62 (± 4.6)	4	17
0.0017	12	21 (± 1.4)	-6	0
0	12	—	-10	0

Source: Reset from Stover 1981.

2. Other Animal Experiments

Only a few other reasonably complete effects studies of short-lived bone-seeking thorium isotopes are ready for quoting. One is a German study (Luz et al. 1976). It demonstrated a variety of effects in mice.^(a) They were primarily interested in the ^{224}Ra story, but added ^{227}Th for comparison. They used female mice and gave single or multiple injections of ^{224}Ra and single injections of ^{227}Th .

(a) There were earlier preliminary reports.

At the higher doses, ^{227}Th caused leukemia, which became a primary cause of early death, and also some lesions of the jaw. The incidence of osteosarcoma was considerably higher per rad for ^{227}Th than for ^{224}Ra . There are differences in the anatomical location of the osteosarcomas, with more in the head region at the higher doses.

Some benign tumors (ossifying fibromata) of the jaws also occurred. For these, ^{224}Ra was more effective than ^{227}Th .

There is not much that can be said in explanation of these results, particularly the differences between ^{224}Ra and ^{227}Th . They illustrate amply the greater effectiveness of short-lived isotopes of thorium (and also of radium), presumably because their energy is expended while they are still on or near bone surfaces. There was also early German work on the distribution of thorium to the RES (Engels, Maurer, and Niklas 1949).

Another set of experiments ready for discussion was done in the USSR. This included distribution and excretion, acute toxicity, long-term effects, and detailed examination of the clinical condition of the animals. The work can be found in two translation volumes: Vol. 4 in the series entitled *The Toxicology of Radioactive Substances*, edited by Letavet and Kurlyandskaya (1966) and the large volume edited by Moskalev (paper by Kendysh and Lebedeva [1966] and the one by Kendysh on metabolism already cited). As usual, the USSR work goes into extensive detail on functional changes as well as conventional gross and microscopic pathology. The doses were about 10 mg thorium/kg for single intratracheal administration, 100 mg/kg in intraperitoneal administration, or once weekly up to 1,000 mg/kg. The test animals were rats and rabbits.

Phagocytic function of the RES was clearly depressed after thorium administration as measured by half-life of ^{198}Au in blood and its build-up in spleen and liver. The effect began early and persisted for about a year. The excretory function of the liver, as shown by ^{131}I -labeled rose bengal, was reduced as measured by build-up in the liver and markedly increased half-life. Hepatic blood flow was slowed.

The morphological changes included aggregations of thorium, granulomatous lesions with giant cells containing thorium particles, and vascular changes. Blood changes ranged from early anemia and reticulocytopenia to later leukocytosis.

In general, the intratracheal route of entry was more damaging than the intraperitoneal.

The USSR investigators point out that their doses correspond to only 0.001, 0.01, and 0.1 $\mu\text{Ci/kg}$, and damage is extensive, while plutonium at 0.3 $\mu\text{Ci/kg}$ "does not lead to the development of morphological changes in chronic experiments." On this basis, they conclude that some of the effects of thorium must be due to chemical toxicity. (At that time, the effects of plutonium at the level of 0.3 $\mu\text{Ci/kg}$ had not yet been described.)

In the series of papers in the volume by Letavet-Kurlyandskaya, the range of doses was from 2 to 200 mg/kg; soluble and insoluble compounds were compared, and acute toxicities were determined as well as the long-term effects. Thorium nitrate was the most toxic of the soluble compounds (about 300 mg Th/kg LD_{50}^{30}) with thorium chloride considerably behind (approximately 600 mg Th/kg LD_{50}^{30}). Thorium dioxide was toxicologically inert by comparison. The behavior of thorium dioxide in rat tissues and organs is extensively documented in the first chapter by Syao-Shan (Letavet and Kurlyandskaya 1966).

An interesting clinical observation is the gradual fall in arterial pressure beginning at about nine months after administration. At twelve months, it was lower at 2 mg/kg and 200 mg/kg than at 20, 300, 400, and 1,000 mg/kg. This is a unique observation not mentioned in the studies from other countries. The authors cite studies of thorium workers, which also indicated hypotension and attribute the changes to "disturbance of autonomic regulation."

C. Thoron

It is natural to wonder about the dosages and effects of inhaled thoron by analogy to the effects of inhaled radon. There have been no animal experiments for the obvious reason that thoron (^{220}Rn) has a half-life of only 54.5 sec. Likewise, there is no human epidemiology. Yet, calculations indicate the possibility of exposures to thoron from both thorium metal and thorium ores in storage.

Blanchard and Holaday (1960) at Salt Lake City pursued an analysis very similar to that we saw for radon and its daughters in chapter 3, except that the data were derived from theory and could not be checked by experiment. Duggan (1973), at the National Radiological Protection Board of the United Kingdom, engaged in a similar exercise and made some suggestions for hazard analysis. The results are not like the radon story. The dose from the daughters of radon is much larger (in this case by a factor of seven hundred) than the dose from thoron. Ventilation can play a major role in the fraction of equilibrium attained, but in contrast to the situation with radon, even in quiet air, the ratio of "ThC" to "ThA" is about 0.01 because of the relatively long half-life of "ThB."^(a) Doses to lungs and bronchi from exposure to $10\ \mu\text{Ci}$ of thoron in equilibrium with its daughters could be: from thoron, 4.9×10^{-4} rem/wk to the lungs and 9.5×10^{-4} rem/wk to the bronchi; from the inhaled daughters, 0.35 rem/wk to lungs and 8.7 rem/wk to the bronchi. The latter are obviously not insignificant doses. But internal emitter toxicology efforts have not been extended to significant effects work with thoron.

The nearest we have come to biological studies has been in collection of exhaled thoron. Hursh and Lovaas (1963) describe an ingenious device for measuring thoron exhalation. The gas is collected in a spirometer and then, after passage through a CO_2 and water-vapor trap, enters directly onto a cooled charcoal-particle-covered plate, which is close to a zinc-sulfide-coated disc and a 5-in. photomultiplier tube. Hursh and Lovaas refer also to earlier collection and measurement systems devised by Aub et al. (referred to in chapter 1) and Rundo, Ward, and Jensen (1958). They made measurements of thoron exhalation from two Thorotrast patients and indicate other uses for the system.

Despite the relatively high theoretical doses from inhaled thoron daughters and likely exposures in industry, no systematic investigations of thoron effects in industry have come to the attention of this author. In comparison to the Thorotrast problem, and other members of the thorium series, exposure to thoron and daughters is probably of much less significance.

(a) "ThA" is ^{216}Po , "ThB" is ^{212}Pb , and "ThC" is ^{212}Bi according to the old terminology. This description is no longer used.

VI. Summary and Commentary

This last chapter of the series concerning the naturally occurring radioactive materials considers two elements of importance from the standpoint of health. The other naturally occurring elements are considered below the limits for health concern under normal circumstances.

Polonium, most of whose isotopes are alpha emitters, has had important uses in the atomic energy field and in many devices such as static eliminators. It has never had therapeutic applications. Thorium, which is really a generic name for a large number of isomers, has had much use in industry, e.g., it has been used in the manufacture of gas lamp mantles; a thorium cycle is proposed for nuclear energy to stand beside, perhaps replace, the uranium cycle; and thorium was used extensively in medicine as a component of a radiopaque medium called "Thorotrast."

A. Polonium

It should be mentioned in passing that two of the most energetic and important daughter products of radon are isotopes of polonium. Thus, the radon daughter problem is, in part, a polonium problem. However, it is the longer-lived isotope, ^{210}Po , that has received the most biomedical study.

Polonium contrasts with most of the alpha-emitting radionuclides considered thus far, except radon, in that it does not concentrate in bone to any appreciable extent (unless formed in situ by the decay of ^{210}Pb). It tends to localize in soft tissues. It shows particular propensity to concentrate in elements of the RES due, in part, it seems likely, to its tendency to form radiocolloids. Although the tissue distribution is far from uniform, it is much more like whole-body exposure than that of the bone seekers. Only radon is more like whole-body exposure, but it has an inconveniently short half-life and many complicating decay products. Thus, polonium has been useful for determining generalized soft-tissue effects of alpha particles. They have turned out to be quite different from those of the bone seekers.

Although a small amount of work has been done on polonium in humans, the bulk of the biomedical research has involved animals. The original center was in Lacassagne's laboratory in France. During World War II, the most extensive work was at the University of Rochester, with the addition of some work at Chicago in the latter part of the war years. Just after the war, the facility that had been most involved with the production of polonium, the Dayton Project (which became the Mound Laboratory), and Rochester continued with long-term studies, while the group at Chicago's Argonne National Laboratory completed a long-term study with mice.

Among the key findings with polonium are:

1. The route of administration can make a very large difference in the tissue distribution. This can be attributed to the relative importance of radiocolloids by the several routes of entry.
2. Toxicity varies less with route of administration than does the tissue distribution.
3. A variety of tumors of soft tissue can be induced by polonium.
4. A unique cardiovascular lesion is produced in certain narrow dosage ranges. It consists of thickening of arteriolar walls, obstruction of circulation,

ischemia, and necrosis. When this occurs in the kidney, a typical nephrotoxic syndrome can develop, including hypertension.

5. At high to moderate doses, polonium is more effective biologically than the long-lived bone seekers. However, at long times, it is about equal to radium in broad terms.
6. Results from tracer studies with five hospitalized patients at Rochester indicated distribution and excretion similar to that worked out in the animal experiments.

In more recent years, there has been considerable interest in the possible role of polonium that gathers naturally on tobacco leaves in the etiology of lung cancer in cigarette smokers. This has not been settled definitively.

There are significant amounts of naturally occurring polonium in the environment. Work done in the marine environment indicates the presence of very high concentrations in certain sea plants and fish viscera.

The pressure for further biomedical work with polonium has eased. It is no longer manufactured in quantity for the military, and better sources have been worked out for static eliminators. It is the possible role in the effects of tobacco smoke or inhaled radon daughter products that keeps interest in this element alive, plus its usefulness as a tool to study alpha-particle effects.

B. Thorium

The biomedical as well as the physical and chemical stories with thorium, and the members of its decay series, are far more complex than those with polonium. Thorium isomers are still used in industry, and the long-term effects of Thorotrast in man are still being worked out. The complex decay chain has made work with the thorium series much more difficult than work with most of the other radionuclides discussed in this book. We have, indeed, seen the dilemma of having one set of experiments that seemed to prove that thorium was all but inert toxicologically, and others that place it close to plutonium in relative toxicity. It all depends on which isomer is being dealt with and at which point in the decay series one enters.

Animal work involving thorium has been rather diffuse. Rochester, NYU, and the University of Utah have been the principal contributors in the United States.

The broadest effort has gone into study of the Thorotrast cases. Many thousands of individuals, especially in Europe, received this radiopaque medium before its propensity to remain in situ indefinitely and eventually to produce cancer in soft tissues was realized. Several discrete populations have been under study: three are in Europe (Denmark, Portugal, and West Germany), one is in Japan, and there are less homogeneous groups in the United States. It was thought that these would provide epidemiologic data comparable to the radium story. They have not, at least not yet. Dosimetry is very difficult, a possible factor of potential chemical toxicity is only now approaching resolution, and more time is obviously needed to get complete information on the pertinent populations. We can expect this to occupy future endeavors.

Some animal work on Thorotrast was done at NYU, Rochester, and Utah, but this too, requires extension.

On the whole, many dilemmas persist with thorium. If a thorium fuel cycle should receive serious attention, we can expect a resurgence of work in the field. If not, we can hope for continuation of the Thorotrast studies to their logical conclusion, but not very much more.

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Polonium Report No. TID-5221
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Note 2—Table of Contents

Metabolism and Biological Effects of an Alpha Particle Emitter, Polonium-210

Radiation Research, Supplement 5, 1964

Co-editors: J. Newell Stannard and George W. Casarett

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- Albert, R. E. 1966. *Thorium: Its industrial hygiene aspects*. New York: Academic Press.
- Albert, R., P. Klevin, J. Fresco, J. Harley, W. Harris, and M. Eisenbud. 1955. Industrial hygiene and medical survey of a thorium refinery. *AMA Arch. Ind. Health* 11:234-42.
- Andervont, H. B. and M. B. Shimkin. 1940. Tumors in mice injected with colloidal thorium dioxide. *J. Nat. Cancer Inst.* 1:349-53.
- Anthony, D. S., R. K. Davis, R. N. Cowden, and W. P. Jolley. 1956. Experimental data useful in establishing maximum permissible single and multiple exposures to polonium. In *Proceedings of the international conference on peaceful uses of atomic energy*, vol. 13, pp. 215-18. Held in Geneva, August 8-20, 1955. New York: United Nations.
- Berke, H. L. and A. C. DiPasqua. 1964. Distribution and excretion of polonium-210. VIII. After inhalation by the rat. *Radiat. Res. Suppl.* 5:133-47.
- Blair, H. A. 1964. The shortening of life span by a single injection of radium, plutonium, or polonium. *Radiat. Res. Suppl.* 5:216-27.
- Blanchard, R. L. 1967. Concentrations of ^{210}Pb and ^{210}Po in human soft tissues. *Health Phys.* 13:625-32.
- Blanchard, R. L. and D. A. Holaday. 1960. Evaluation of radiation hazards created by thoron and thoron daughters. *Am. Ind. Hyg. Assoc. J.* 21:201-06.
- Boecker, B. B. 1963. Thorium distribution and excretion studies. III. Single inhalation exposure to the citrate complex and multiple inhalation exposures to the chloride. *Am. Ind. Hyg. Assoc. J.* 24:155-63.
- Boecker, B. B., R. G. Thomas, and J. K. Scott. 1963. Thorium distribution and excretion studies. II. General patterns following inhalation and the effect of the size of the inhaled dose. *Health Phys.* 9:165-76.
- Boone, I. U., B. S. Rogers, D. C. White, and P. S. Harris. 1958. Toxicity, excretion and tissue distribution of ionium (Th^{230}) in rats. *Am. Ind. Hyg. Assoc. J.* 19:285-95.
- Boyd, G. A. and R. M. Fink. 1950. Discussion of lethal-dosage data. Part 6 of chapter 8 in Fink 1950, pp. 333-43.
- Boyd, G. A., H. E. Silberstein, and R. M. Fink. 1950. Studies with polonium. Part 2 of chapter 7 in Fink 1950, pp. 213-23.
- Brucer, M. 1981. Unraveling the natural decay series. In *Vignettes of Nuclear Medicine*, no. 97. St. Louis: Mallinckrodt, Inc.
- Callihan, D. and D. Ross. 1952. *A review of a polonium contamination problem*. ORNL-1381 (rev.), issued August 12, 1952, declassified May 1, 1956. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Campbell, J. E., E. S. Robajdek, and D. S. Anthony. 1956. The metabolism of Ac^{227} and its daughters Th^{227} and Ra^{223} by rats. *Radiat. Res.* 4:294-302.
- Campbell, J. E. and L. H. Talley. 1954. Association of polonium-210 with blood. *Proc. Soc. Exp. Biol. Med.* 87:221-23.
- Casarett, G. W. 1952. *Histopathology of alpha radiation from internally administered polonium*. UR-201. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Casarett, G. W. 1964a. Hematology of single intravenous doses of polonium. *Radiat. Res. Suppl.* 5:322-46.
- Casarett, G. W. 1964b. Pathology of multiple intravenous doses of polonium. *Radiat. Res. Suppl.* 5:347-60.
- Casarett, G. W. 1964c. Pathology of orally administered polonium. *Radiat. Res. Suppl.* 5:361-72.
- Casarett, G. W. 1964d. Pathology of single intravenous doses of polonium. *Radiat. Res. Suppl.* 5:246-321.
- Casarett, G., R. G. Metcalf, and G. A. Boyd. 1950. Pathology studies on rats injected with polonium, plutonium, and radium. Part 7 of chapter 8 in Fink 1950, pp. 343-88.
- Casarett, L. J. 1964a. Distribution and excretion of polonium-210. V. Autoradiographic study of effects of route of administration on distribution of polonium-210. *Radiat. Res. Suppl.* 5:93-105.

- Casarett, L. J. 1964b. Distribution and excretion of polonium-210. IX. Deposition, retention, and fate after inhalation by "nose-only" exposure, with notes on mechanics of deposition and clearance and comparison of routes of administration. *Radiat. Res. Suppl.* 5:148-65.
- Cohen, B. S. 1979. *The magnitude, lung distribution and significance of the polonium-210 inhaled in cigarette smoke*. Dissertation, New York Univ., Graduate School of Arts and Science.
- Cohen, B. S., M. Eisenbud, M. E. Wrenn, and N. H. Harley. 1978. Distribution of polonium-210 in the human lung. *Health Phys.* 35:898.
- Cohen, B. S., M. Eisenbud, M. E. Wrenn, and N. H. Harley. 1979. Distribution of polonium-210 in the human lung. *Radiat. Res.* 79:162-68.
- Cohn, S. H., E. A. Gusmano, and J. S. Robertson. 1967. Calculation of radiation dose from Thorotrast using whole-body gamma-ray spectral data. *Ann. N.Y. Acad. Sci.* 145: 608-22.
- Cowden, R. N. 1952. *Histopathological study of Sprague-Dawley rats injected intravenously with varying amounts of polonium*. MLM-761, issued April 1, 1952, declassified November 19, 1955. Miamisburg, Ohio: Mound Laboratory.
- Cowden, R. N. and R. E. Zipf. 1956. Histopathological and hematological effects. Section 3.2 of chapter 5 in Moyer, Gagey, and Rogers 1956, pp. 110-12.
- Cuthbert, F. L. 1950. *Thorium production technology*. Reading, Mass.: Addison-Wesley Publishing Co.
- Davis, R. K., W. T. Rockhold, and D. S. Anthony. 1954. *The effects of repeated polonium injections on rats: I. Gross effects and metabolism of 2 μ C/kg doses*. MLM-961, p. 31. Miamisburg, Ohio: Mound Laboratory.
- Davis, R. K. and G. L. Stevenson. 1954. *The effects of routes of administration upon the distribution of polonium in the rat*. Quarterly progress report, MLM-989, p. 7. Miamisburg, Ohio: Mound Laboratory.
- Della Rosa, R. J. and J. N. Stannard. 1964. Acute toxicity as a function of route of administration. *Radiat. Res. Suppl.* 5:205-15.
- Dougherty, J. H. and L. S. Rosenblatt. 1971. Long-term hematological effects of internal emitters in beagles. *Radiat. Res.* 48:319-31.
- Downs, W. L., J. K. Scott, E. A. Maynard, and H. C. Hodge. 1959. *Studies on the toxicity of thorium nitrate*. UR-561. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Dudley, R. A. 1967. A survey of radiation dosimetry in thorium dioxide cases. *Ann. N.Y. Acad. Sci.* 145:595-607.
- Duggan, M. J. 1973. Some aspects of the hazard from airborne thoron and its daughter products. *Health Phys.* 24:301-10.
- Engels, A., W. Maurer, and A. Niklas. 1949. Einige Versuche zur Thoriumresorption im Reticuloendothelialen System. *Z. Gesamte Exp. Med.* 115:221-28.
- Faber, M. 1968. Epidemiology experience with Thorotrast in Denmark. In *The Dosimetry and toxicity of Thorotrast*, IAEA Technical Report 106, pp. 139-46. Proceedings of a symposium held in Vienna, October 4-7, 1965. Vienna: International Atomic Energy Agency.
- Feldman, I. and P. Saunor. 1964. Some *in vitro* studies of polonium-210 binding by blood constituents. *Radiat. Res. Suppl.* 5:40-48.
- Fernau, A., Schramek, and Zarzycki. 1913. Über Wirkung von Polonium. *Strahlentherapie* 3:333-42.
- Fink, R. M. 1950. *Biological studies with polonium, radium, and plutonium*. National Nuclear Energy Series, div. VI, vol. 3. New York-Toronto-London: McGraw-Hill.
- Finkel, M. P. and G. M. Hirsch. 1954. *Progress of the polonium mouse experiment. II. Analysis at 500 days*. ANL-4531, pp. 80-92. Argonne, Ill.: Argonne National Laboratory.
- Finkel, M. P., W. E. Kisielski, G. M. Hirsch, and T. J. Mulhaney. 1949. *Polonium and CF-1 female mice: The 30-day LD₅₀, retention, distribution, and concentration*. Quarterly progress report, ANL-4333, pp. 84-96. Argonne, Ill.: Argonne National Laboratory.
- Finkel, M. P., W. P. Norris, W. E. Kisielski, and G. M. Hirsch. 1953. The toxicity of polonium 210 in mice. I. The thirty day LD₅₀, retention, and distribution. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* 70:477-85.

- Folsom, T. R., K. M. Wong, and V. F. Hodge. 1972. Extreme accumulations of natural polonium-210 in certain marine organisms. In *The natural radiation environment II*, eds. J. A. S. Adams, W. M. Lowder, and T. F. Gesell, CONF-720805-P2, pp. 863-82. Proceedings of a symposium held in Houston, Tex., August 7-11, 1972. Washington, D.C.: Energy Research and Development Administration.
- Gallimore, J. C., G. A. Boyd, and J. N. Stannard. 1954. An autoradiographic study of the distribution of polonium in the rat during 24 hours after intravenous injection. *Anat. Rec.* 118:253-74.
- Gorham, A. T., R. M. Fink, C. P. Kimball, W. L. Minto, H. E. Silberstein, E. K. Vittum, W. F. Bale, T. Enns, and E. L. Alling. 1950. General methods used in polonium distribution and excretion experiments. Chapter 1 in Fink 1950, pp. 7-34.
- Gustafson, P. F., L. D. Marinelli, and E. A. Hathaway. 1957. A case of accidental puncture contaminated with Th^{227} . Studies on elimination and residual body activity. *Radiology* 68:358-65.
- Haissinsky, M. 1961. *Polonium*. A translation by R. C. Lange from *Nouveau traité de chimie minérale*, 13, pt. 2. Paris: Masson. [Issued in 1964 as MLM-1165 (Tr).] Miamisburg, Ohio: Mound Laboratory.
- Hamilton, J. G. 1947. The metabolism of the fission products and the heaviest elements. *Radiology* 49:325-43.
- Harley, N. et al. 1979. *Investigation of polonium-210 as a risk factor in smoking related carcinogenesis*. N. Y. U. Institute of Environmental Medicine, 16th Annual Report, pp. 130-34.
- Hill, C. R. 1965. Polonium-210 in man. *Nature* 208:423-28.
- Hodge, H. C., E. A. Maynard, and L. J. Leach. 1960. *The chemical toxicity of thorium dioxide following inhalation by laboratory animals*. UR-562. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Hodge, H. C. and R. G. Thomas. 1959. The questions of health hazards from the inhalation of insoluble uranium and thorium oxides. In *Progress in nuclear energy*, eds. W. G. Marley and K. Z. Morgan, ser. 12, Health Physics, vol. 1, pp. 52-59 (Geneva Conference paper [1958] P/739). New York: Pergamon Press.
- Hoffman, F. L., V. F. Hodge, and T. R. Folsom. 1974. Polonium radioactivity in certain mid-water fish of the eastern temporal Pacific. *Health Phys.* 26:65-70.
- Holtzman, R. B., H. Spencer, F. H. Ilcewicz, and L. Kramer. 1974. Metabolic balances of ^{210}Pb and ^{210}Po in unexposed men. In *Proceedings of the 3d international congress of the International Radiation Protection Association*, ed. W. S. Snyder, CONF-730907-P2, pp. 1406-11. Held in Washington, D.C., September 9-14, 1973. Oak Ridge, Tenn.: Technical Information Center.
- Hursh, J. B. 1967. Loss of thorium daughter by thorium dioxide patients. *Ann. N.Y. Acad. Sci.* 145:634-41.
- Hursh, J. B. 1974. An argument against the use of the special curie for natural uranium and natural thorium. *Health Phys.* 27:147-52.
- Hursh, J. B. and A. Lovaas. 1963. A device for measurement of thoron in the breath. *Health Phys.* 9:621-27.
- Hursh, J. B., L. T. Steadman, W. B. Looney, and M. Colodzin. 1957. The excretion of thorium and thorium daughters after Thorotrast administration. *Acta Radiol.* 47:481-98.
- Ibrahim, S. A., M. E. Wrenn, N. P. Singh, N. Cohen, and G. Saccomano [sic]. 1983. Thorium concentration in human tissues from two U.S. populations. *Health Phys.* 44 Suppl. 1:213-20.
- ICRP. See International Commission on Radiological Protection.
- International Commission on Radiological Protection. 1959. *Recommendations of the ICRP*. Publ. no. 2. Report of Committee II on permissible dose for internal radiation. New York-London: Pergamon Press.
- International Commission on Radiological Protection. 1979. *Limits for intakes of radionuclides by workers*. Publ. 30, supplement to part 1, Ann. ICRP, vol. 3, no. 1-4. Oxford: Pergamon Press.

- International Symposium. 1963. *Proceedings of the thorium fuel cycle symposium*, TID-7650, books I and II. Held in Gatlinburg, Tenn., December 5-7, 1962. Washington, D.C.: Department of Commerce, Office of Technical Services.
- International Symposium. 1965. *Panel on the utilization of thorium in power reactors*, STI/DOC/10/52. Vienna: International Atomic Energy Agency.
- International Symposium. 1968. Thorium fuel cycle. In *Proceedings of the 2d international thorium fuel cycle symposium*, CONF-660524. Held in Gatlinburg, Tenn., May 3-6, 1966. Oak Ridge, Tenn.: Technical Information Center.
- Jee, W. S. S., M. H. Bartley, N. L. Dockum, J. Gee, and G. H. Kenner. 1969. Vascular changes in bones following bone-seeking radionuclides. In *Delayed effects of bone-seeking radionuclides*, eds. C. W. Mays, W. S. S. Jee, R. D. Lloyd, B. J. Stover, J. H. Dougherty, and G. N. Taylor, pp. 437-55. Salt Lake City: Univ. of Utah Press.
- Jee, W. S. S., G. A. Kenner, M. H. Bartley, N. L. Dockum, M. Sah, H. Mueller, and K. Scheffrahn. 1967. Preliminary report: Changes in vascularity of cortical bones induced by bone seeking radionuclides. In *Research in radiobiology annual report of work in progress in the Internal Irradiation Program*. COO-119-236, pp. 97-125. Salt Lake City: Univ. of Utah Press.
- Kauranen, P. and J. K. Miettinen. 1967. ^{210}Po and ^{210}Pb in environmental samples in Finland. In *Radioecological concentration processes*, eds. B. Åberg and F. P. Hungate, pp. 275-80. Proceedings of a symposium held in Stockholm, April 25-29, 1966. Oxford-London-New York: Pergamon Press.
- Kendrysh, I. N. 1966. Distribution and elimination of ^{232}Th . In *Distribution and biological effects of radioactive isotopes*, ed. Yu. I. Moskalev, AEC-tr-6944, pp. 25-34. Moscow: Atomizdat.
- Kendrysh, I. N. and G. A. Lebedeva. 1966. Biological effect of nitrate ^{232}Th . In *Distribution and biological effects of radioactive isotopes*, ed. Yu. I. Moskalev, AEC-tr-6944, pp. 359-74. Moscow: Atomizdat.
- Lanz, H., K. G. Scott, J. Crowley, and J. Hamilton. 1946. *The metabolism of thorium, protactinium, and neptunium in the rat*. Metallurgical Laboratory Report CH-3606, August 1946, declassified October 1955.
- Lanzola, E. E., M. E. Allegrini, and D. M. Taylor. 1973. The binding of polonium-210 to rat tissues. *Radiat. Res.* 56:370-84.
- Lapp, R. E. and H. L. Andrews. 1972. *Nuclear radiation physics*. 4th ed. Englewood Cliffs, N.J.: Prentice-Hall, Inc.
- Letavet, A. A. and E. B. Kurlyandskaya, eds. 1966. *The toxicology of radioactive substances. IV. Thorium-232 and uranium-238*, translated by A. Crozy, pp. 1-82. Translation edited by G. W. Dolphin. New York-London: Pergamon Press.
- Little, J. B., E. P. Radford, Jr., H. L. McCombs, V. R. Hun, and C. Nelson. 1964. Polonium-210 in lungs and soft tissues of cigarette smokers. *Radiat. Res.* 22:209.
- Looney, W. B. 1960. An investigation of the late clinical findings following Thorotrast (thorium dioxide) administration. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* 83:163-85.
- Luz, A., W. A. Müller, W. Gössner, and O. Hug. 1976. Estimation of tumour risk at low dose from experimental results after incorporation of short-lived bone-seeking alpha emitters ^{224}Ra and ^{227}Th in mice. In *Biological and environmental effects of low-level radiation*, STI/PUB/409, vol. 2, pp. 171-81. Proceedings of a symposium held in Chicago, November 3-7, 1975. Vienna: International Atomic Energy Agency.
- Maletskos, C. J., A. T. Keane, N. C. Telles, and R. D. Evans. 1969. Retention and absorption of ^{224}Ra and ^{234}Th in human beings. In *Delayed effects of bone-seeking radionuclides*, eds. C. W. Mays, W. S. S. Jee, R. D. Lloyd, B. J. Stover, J. H. Dougherty, and G. N. Taylor, pp. 29-49. Salt Lake City: Univ. of Utah Press.
- Martell, E. A. 1974. Radioactivity of tobacco trichomes and insoluble cigarette smoke particles. *Nature* 249:215-17.
- Mattis, P. A. 1950. *Western Reserve University School of Medicine Atomic Energy Project*. NYO 1607.
- May, H., L. D. Marinelli, and J. B. Corcoran. 1967. In vivo counting of thorium dioxide patients: Special techniques and preliminary results. *Ann. N.Y. Acad. Sci.* 145:623-33.

- Mays, C. W. 1979. Liver cancer risk. In *Biological implications of radionuclides released from nuclear industries*, STI/PUB/522, vol. 2, pp. 147-65. Proceedings of a symposium held in Vienna, March 26-30, 1979. Vienna: International Atomic Energy Agency.
- Mays, C. W., R. Haldin, and M. A. Van Dilla. 1958. Thoron exhalation in radiothorium-burdened beagles. *Radiat. Res.* 9:438-44.
- Mays, C. W. and R. D. Lloyd. 1972. Bone sarcoma incidence vs. alpha particle dose. In *Radiobiology of plutonium*, eds. B. J. Stover and W. S. S. Jee, pp. 409-30. Salt Lake City: The J. W. Press.
- Mays, C. W., T. H. Dougherty, G. N. Taylor, R. D. Lloyd, B. J. Stover, W. S. S. Jee, W. R. Christiansen, J. H. Dougherty, and D. R. Atherton. 1969. Radiation-induced bone cancer in beagles. In *Delayed effects of bone-seeking radionuclides*, eds. C. W. Mays, W. S. S. Jee, R. D. Lloyd, B. J. Stover, J. H. Dougherty, and G. N. Taylor, pp. 387-408. Salt Lake City: Univ. of Utah Press.
- Metcalf, R. G., G. Casarett, and G. A. Boyd. 1950. Pathology studies on rats injected with polonium, plutonium, and radium. Part 6 of chapter 7 in Fink 1950, pp. 257-82.
- Mole, R. H. 1978. The radiobiological significance of the studies with ^{224}Ra and Thorotrast. *Health Phys.* 35:167-74; also *Env. Res.* 18:192-215, 1979.
- Moroz, B. B. and Yu. D. Parfenov. 1972a. *Effects of polonium-210 on the organism*. AEC-tr-7300. Oak Ridge, Tenn.: Technical Information Center. [Moscow: Atomizdat, 1971.]
- Moroz, B. B. and Yu. D. Parfenov. 1972b. Metabolism and biological effects of polonium-210. *At. Energy Rev.* 10:175-232.
- Morrow, P. E. and R. J. Della Rosa. 1964. Distribution and excretion of polonium-210. VII. Fate of polonium colloid after intratracheal administration to rabbits. *Radiat. Res. Suppl.* 5:124-32.
- Morrow, P. E., R. J. Della Rosa, L. J. Casarett, and G. J. Miller. 1964a. Investigations of the colloidal properties of polonium-210 solutions using molecular filters. *Radiat. Res. Suppl.* 5:1-15.
- Morrow, P. E., F. A. Smith, R. J. Della Rosa, L. J. Casarett, and J. N. Stannard. 1964b. Distribution and excretion of polonium-210. II. The early fate in cats. *Radiat. Res. Suppl.* 5:60-66.
- Moyer, H. V., L. G. Gnagey, and A. J. Rogers, eds. 1956. *Polonium*. TID-5221, Oak Ridge, Tenn.: Technical Information Service Extension.
- Naimark, D. H. 1948. *Acute exposure to polonium (medical study of three human cases)*. MLM-67, written March 1948, declassified June 25, 1958. Miamisburg, Ohio: Mound Laboratory.
- National Council on Radiation Protection and Measurements. 1959. *Maximum permissible body burdens and maximum permissible concentrations of radionuclides in air and in water for occupational exposure*. Report no. 22, National Bureau of Standards Handbook 69. Washington, D.C.
- National Council on Radiation Protection and Measurements. 1975. *Natural background radiation in the United States*. Report no. 45, Washington, D.C.
- National Council on Radiation Protection and Measurements. 1986. *Exposure of the population in the United States to ionizing radiation*. Draft report of Scientific Committee-48. [To be published after Council review as an NCRP report. Details may be changed in the review.]
- NCRP. See National Council on Radiation Protection and Measurements.
- Oberling, C. and M. Guérin. 1933. Action du Thorotrast sur le sarcome de Jensen du rat blanc. *Bull. Assoc. Fr. Etude Cancer* 22:469-89.
- Parr, R. M. 1967. Information on Thorotrast dosimetry supplied by the radiochemical analysis of tissue specimens. *Ann. N.Y. Acad. Sci.* 145:644-53.
- Parr, R. M., H. F. Lucas, Jr., and M. L. Griem. 1969. Metabolism of ^{232}Th decay series, radionuclides in man and other animals following intravascular administration of Thorotrast. In *Argonne National Laboratory annual report*, ANL-7615, pp. 97-115. Argonne, Ill.: Argonne National Laboratory.
- Radford, E. P., Jr., and V. R. Hunt. 1964. Polonium-210: A volatile radioelement in cigarettes. *Science* 143:247-49.

- Radford, E. P., Jr., V. R. Hunt, and J. B. Little. 1964. [Comment on letter by Skrable, Haughey, and Alexander.] *Science* 146:87.
- Radford, E. P. and E. A. Martell. 1976. Polonium-210:lead-210 ratios as an index of residence times of insoluble particles from cigarette smoke in bronchial epithelium. In *Inhaled particles IV*, pt. 2, pp. 567-81. Proceedings of a symposium held in Edinburgh, September 22-26, 1975. Oxford: Pergamon Press.
- Rajewsky, B. and W. Stahlhofen. 1966. Polonium-210 activity in the lungs of cigarette smokers. *Nature* 209:1312-13.
- Robertson, M. K. and M. W. Randle. 1974. Hazards from the industrial use of radioactive static eliminators. *Health Phys.* 26:245-50.
- Rotblat, J. and G. B. Ward. 1953. Tissue dosage from Thorotrast in the body. *Nature* 172:769-70.
- Rundo, J. 1955. Considerations of the limits of radiation dosage from Thorotrast. *Br. J. Radiol.* 28:615-19.
- Rundo, J., P. Failla, and R. A. Schlenker, eds. 1983. *Radiobiology of radium and the actinides in man*. Proceedings of an international conference held in Lake Geneva, Wisc., October 11-16, 1961. *Health Phys.* 44 Suppl. 1.
- Rundo, J., A. H. Ward, and P. G. Jensen. 1958. Measurement of thoron in the breath. *Phys. Med. Biol.* 3:101-10.
- Samuels, L. D. 1966. Depletion of mouse spermatogonia following exposure to polonium-210. *Nature* 210:434-35.
- Scott, J. K., W. F. Neuman, and J. F. Bonner. 1952. The distribution and excretion of thorium sulphate. *J. Pharmacol. Exp. Ther.* 106:286-90.
- Scott, J. K. and J. N. Stannard. 1954. Relationship between *Bartonella muris* infection and acute radiation effects in the rat. *J. Infect. Dis.* 95:302-08.
- Scott, L. M. and C. M. West. 1975. Excretion of 210-Po oxide following accidental inhalation. *Health Phys.* 28:563-65.
- Selbie, F. R. 1936. Experimental production of sarcoma with Thorotrast. *Lancet* 231:847-48.
- Selbie, F. R. 1938. Tumours in rats and mice following the injection of Thorotrast. *Br. J. Exp. Pathol.* 19:100-07.
- Silberstein, H. E. 1950. Introduction to "Distribution and Excretion of Polonium." Part I in Fink 1950, pp. 3-6.
- Silberstein, H. E., W. L. Minto, R. M. Fink, G. A. Boyd, R. G. Metcalf, W. Mann, C. P. Kimball, and A. T. Gorham. 1950. Polonium distribution and excretion experiments with animals. Chapter 2 in Fink 1950, pp. 35-121.
- Skrable, K. W., F. J. Haughey, and E. L. Alexander. 1964. Polonium-210 in cigarette smokers. *Science* 146:86.
- Smith, F. A., P. E. Morrow, F. R. Gibb, R. J. Della Rosa, L. J. Casarett, J. K. Scott, D. A. Morken, and J. N. Stannard. 1961. Distribution and excretion studies in dogs exposed to an aerosol containing polonium-210. *Am. Ind. Hyg. Assoc. J.* 22:201-08.
- Spiess, H. and C. W. Mays. 1973. Protraction effect on bone-sarcoma induction of ²²⁴Ra in children and adults. In *Radionuclide carcinogenesis*, eds. C. L. Sanders, R. H. Busch, J. E. Ballou, and D. D. Mahlum, CONF-720505, pp. 437-50. Proceedings of the 12th annual Hanford life sciences symposium held in Richland, Wash., May 10-12, 1972. Springfield, Va.: National Technical Information Service.
- Spoerl, E. and D. S. Anthony. 1956. Biological research related to polonium. Chapter 5 in Moyer, Gnagey, and Rogers 1956, pp. 97-115.
- Sproul, J. A., R. C. Baxter, and L. W. Tuttle. 1964. Some late physiological changes in rats after polonium-210 alpha-particle irradiation. *Radiat. Res. Suppl.* 5:373-88.
- Stannard, J. N. 1964. Distribution and excretion of polonium-210. I. Comparison of oral and intravenous routes in the rat. *Radiat. Res. Suppl.* 5:49-59.
- Stannard, J. N., H. A. Blair, and R. C. Baxter. 1964. Mortality, life span, and growth of rats with a maintained body burden of polonium. *Radiat. Res. Suppl.* 5:228-45.
- Stannard, J. N. and G. W. Casarett, eds. 1964. Metabolism and biological effects of an alpha particle emitter, polonium-210. *Radiat. Res. Suppl.* 5.

- Stannard, J. N. and F. A. Smith. 1964. Distribution and excretion of polonium-210. X. Species comparison. *Radiat. Res. Suppl.* 5:166-74.
- Stenstrom, W. 1941. Elimination of radioactive elements by patients and rabbits after injection of thorotrast. *Radiology* 37:698-704.
- Stover, B. J. 1981. Toxicology of ^{228}Th in young adult beagles: Potential relationship to the thorium fuel cycle. In *Actinides in man and animals*, ed. M. E. Wrenn, pp. 483-92. Proceedings of the Snowbird actinide workshop held in Snowbird, Utah, October 15-17, 1979. Salt Lake City: RD Press.
- Stover, B. J., D. R. Atherton, and C. W. Mays. 1962. Studies of the retention and distribution of Ra^{226} , Pu^{239} , $\text{Ra}^{228}(\text{MsTh})$, $\text{Th}^{228}(\text{RaTh})$, and Sr^{90} in adult beagles. In *Some aspects of internal irradiation*, eds. T. F. Dougherty, W. S. S. Jee, C. W. Mays, and B. J. Stover, pp. 7-25. Proceedings of a symposium held in Heber, Utah, May 8-11, 1961. New York-Oxford: Pergamon Press.
- Stover, B. J., D. R. Atherton, D. S. Buster, and N. Keller. 1965. The Th^{228} decay series in adult beagles: Ra^{226} , Pb^{212} , and Bi^{212} in blood and excreta. *Radiat. Res.* 26:226-43.
- Sultzter, M. and J. B. Hursh. 1954. Polonium in urine of miners exposed to radon. *Arch. Ind. Hyg. Occup. Med.* 9:89-100.
- Svirbely, J. L. 1949. *Effective half-life of polonium in the human*. MLM-272, issued January 25, 1949, declassified March 19, 1958. Miamisburg, Ohio: Mound Laboratory.
- Tarasenko, N. Yu. 1963. *Industrial health in handling thorium*. AEC-tr-6536 (rev.). [Translated from a publication of Gosatomizdat, Moscow, 1963.] Springfield, Va: U.S. Department of Commerce, National Bureau of Standards.
- Tessmer, C. F. and J. P. Chang. 1967. Thorotrast localization by light and electron microscopy. *Ann. N.Y. Acad. Sci.* 145:545-75.
- Thomas, R. G. 1957. *The metabolism of thorium-230 (ionium) administered by intratracheal injection to the rat*. UR-480. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Thomas, R. G. 1961. *Distribution and excretion of thorium with emphasis upon route of injection and amount of carrier present*. UR-592. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Thomas, R. G. 1964. The binding of polonium by red cells and plasma proteins. *Radiat. Res. Suppl.* 5:29-39.
- Thomas, R. G., R. Lie, and J. K. Scott. 1963. Thorium distribution and excretion studies. I. Patterns following parenteral administration. *Health Phys.* 9:153-63.
- Thomas, R. G. and J. N. Stannard. 1964a. Distribution and excretion of polonium-210. VI. After intratracheal administration in the rat. *Radiat. Res. Suppl.* 5:106-23.
- Thomas, R. G. and J. N. Stannard. 1964b. Influence of physicochemical state of intravenously administered polonium-210 on uptake and distribution. *Radiat. Res. Suppl.* 5:16-22.
- Thomas, R. G. and J. N. Stannard. 1964c. Some characteristics of polonium solutions of importance in biological experiments. *Radiat. Res. Suppl.* 5:23-28.
- Tuttle, L. W. and R. C. Baxter. 1964. Effect of polonium alpha-particle irradiation on reticuloendothelial function in the rat. *Radiat. Res. Suppl.* 5:389-97.
- United Kingdom Polonium Symposium 1970. *Biology and ecology of polonium and radiolead*. Held at Sutton, Surrey. [Abstracts available from attendees but never published.]
- Wong, K. M., V. F. Hodge, and T. R. Folsom. 1972. Plutonium and polonium inside giant brown algae. *Nature* 237:460-62.
- Wrenn, M. E. 1977. Statement for the record, subcommittee on the environment and the atmosphere, House of Representatives Committees on Science and Technology, September 29, 1977.
- Wrenn, M. E., N. P. Singh, and G. Saccomanno. 1983. Uranium and thorium isotopes and their state of equilibria in lungs from uranium miners. In *Health Phys.* 44 Suppl. 1:385-89.
- Wrenn, M. E., N. P. Singh, M. Cohen, S. A. Ibrahim, and G. Saccomanno. 1981. *Thorium in human tissues*. NUREG/CR-1227. Washington, D.C.: U.S. Nuclear Regulatory Commission.

Preface to Section II

The Manmade Radioisotopes

The four chapters in this section involve the most active period in nuclear science; in some respects the most active period in all of scientific history. It goes from the first small-scale demonstrations of transmutation of the elements by radiations from naturally occurring radionuclides; through the production of radioisotopes by various accelerators, such as the cyclotron; the discovery and applications of nuclear fission with the production of thousands of new radioisotopes; the production of plutonium and other transuranic elements; the atomic bomb and the widespread applications of nuclear energy in the affairs of man. These events have been chronicled in depth elsewhere. A few of the key nonbiological events will be set down in these chapters largely for orientation purposes. The primary focus will be, of course, on biomedical aspects.

In contrast to the rather plodding pace of work with naturally occurring radionuclides during the earlier decades of the twentieth century, the work on manmade isotopes developed with amazing rapidity. Part of this was, of course, the stimulus of World War II, but the pace in the 1930s was also rapid. Sheer enthusiasm for what could be done with the new high-energy accelerators created the environment for rapid development of new techniques, new fields, and new applications. This included biology and medicine.

To a degree, all the remainder of this book considers manmade isotopes more than those that occur naturally. Yet we have already seen that the naturally occurring radionuclides are still of interest and importance. Thus, later sections will sometimes involve both manmade and natural radionuclides as is convenient to the subject at hand.

In contrast to the depictions of the series of naturally occurring radionuclides in the preface to the previous section, we reserve discussion of the major categories of these new isotopes for the individual chapters. Such discussions need to be close to the discussions of biology. In chapter 6, the general characteristics of the fission products and their production are described briefly. In chapter 7, we trace the remarkable progression in development of the actinides—so-called by Seaborg because they were considered to be chemically related to actinium—from an unweighable invisible source of activity to kilograms, even tons, and how the biomedical community kept up with these rapid-fire developments.

The decade of the 1930s saw the new accelerators pressed into service for production of radioisotopes for many purposes. Included was their use as

tracers for biochemical reactions, for physiological functions and the beginnings of nuclear medicine. It was an exciting decade for "basic" research. There was unusually close liaison, indeed collaboration, between the physicists and the biologists and physicians. Chapter 5 gives a brief review of the developments most pertinent to our mission and of the flavor of the 1930s.

The period of World War II is reviewed under two headings "New Dimension Number One—the Fission Products" and "New Dimension Number Two—The Actinides and Transuranium Elements." This was a period of frenetic activity for the biomedical community as much as for the physicists, chemists, and engineers. No one knew whether or not the Germans had made headway with the development of atomic weapons. There was much suspicion that they might have since the basic phenomena of nuclear fission had been discovered and described in Germany. The haste to "beat the Nazis to it" that motivated what became the Manhattan Engineer District (MED) was felt just as keenly by those who wanted to know something about the biomedical properties and effects of the new families of radionuclides expected to be produced. The progression, while not as dramatic as the development of the first chain-reacting "pile," etc., was full of new vistas that took not only the war years but several postwar decades to follow through on. Chapters 6 and 7 consider this era with special emphasis on reporting some of the wartime work that did not get published (see general preface and Appendix C).

The conditions of work during the years of World War II were far from luxurious. Seaborg's diagrams and pictures of the floor plans of his laboratories in the Metallurgical Laboratory buildings at Chicago show space allotted to senior chemists with enormous responsibilities that a present day undergraduate would find cramped (Seaborg 1977).^(a) Furthermore, salaries were uniform and no more than adequate. Research associates (senior investigators with Ph.D. degrees and considerable experience) might get as much as \$350 per month, a fresh Ph.D. \$250 per month, a research assistant \$225 per month, a B.S. degree chemist with experience \$150 per month, etc. Faculty members from universities were offered a 20% boost over their current salary and a small cost-of-living allowance (Seaborg 1977). They worked a full six-day week, including Thanksgiving, and many an entry in the Seaborg papers shows meetings and experiments on Sunday. It is true that expenses were low too. Seaborg notes his round-trip train fare to Buffalo from Chicago for a meeting at under \$40 with Pullman accommodations. He notes a round-trip to Urbana for about \$9, and his hotel there cost \$2.25. Thus the salaries went further than you would think.

Under these conditions, the workers could devote every working moment to the task at hand, but there were few luxuries. Nor should there have been. The alternatives were trench or naval warfare, even losing the war. All those with scientific training wanted to use it in the service of their country. Compartmentalization and security measures resulted in only a few key individuals in each group knowing the ultimate purpose of the work. The new elements and compounds had code names, and the biologists theoretically did not know what they were studying. However, surmises could be drawn and were, simply from the nature of the effects seen and the metabolic behavior of the compounds studied. Such surmises were kept to oneself in the MED days.

(a) I am most grateful to Dr. Seaborg for providing me with a copy of this four-volume scientific and anecdotal history of the chemistry section (C-1) of the Metallurgical Laboratory.

Only a relatively fleeting glimpse of all this could be fitted into chapters 6 and 7. Yet it is hoped that they provide guidelines to the major accomplishments (along with those on uranium reviewed in chapters 2 and 9) and entree into the pertinent literature for desired follow-up.

Chapter 8 continues the main threads of the wartime laboratory research on biomedical aspects of the radionuclides, particularly their toxicology, into the postwar decades. It is by far the longest and most detailed chapter in this section. While the MED efforts in biomedicine were concentrated and all-consuming for those involved, the total manpower was not large in comparison to that brought to bear in the postwar years. Also, the effects considered during the war were largely acute effects with only the continuing reminder from the radium cases that long-term chronic effects were lurking in the shadows. The postwar years saw a large expansion of total manpower and budget in order to attack the long-term problems. The experiments became much longer, the ramifications from the war work required far larger staffs, and further new dimensions intruded. I have termed it a "Golden Era" for internal emitter research because there were few constraints except our ignorance of basic mechanisms. It is only partly described in chapter 8. The enormous efforts in inhalation toxicology of radionuclides are considered separately (chapters 9 and 10), and an entire section of five chapters is devoted to the environmental aspects. Thus, this section considers only the laboratory research with manmade radionuclides of the war years and a portion of the laboratory research in the postwar decades.

Chapter 8 includes a fairly detailed description and chronology of the development of the several long-term experiments with radioisotopes developed to approach the long-term effects of relatively low levels of exposure. These were difficult, expensive, and almost unique. Only the efforts with external radiation sources, and the huge genetic experiments with mice at Oak Ridge were comparable. These experiments will never be done again. Therefore, even though the final conclusions are yet to come,^(a) much space is devoted to providing a reasonably comprehensive record of the underlying motivations, the organizations and modus operandi, and the results of these experiments.

It is to be hoped that the region of comparable long-term low-dose effects of chemical toxins in the workplace and in the environment (until recently an area sadly neglected) can benefit from the lessons learned in these large efforts with radionuclides. The longer a concentrated attack on the chemical problems is postponed, the greater are the chances for irreversible damage—a prospect that seems relatively remote in the radionuclide field, barring a nuclear catastrophe. The patience and dedication of hundreds of biomedical scientists should show through in these chapters, along with the wisdom and tolerance of the supporting agencies. This includes the United States Congress, especially the unique Joint Committee on Atomic Energy, and the Division of Biology and Medicine of the Atomic Energy Commission and its successor agencies.

References

- Seaborg, Glenn T. 1977. *History of Met Lab Section C-1—April, 1942 to April, 1943*. Publ. 112, 702 pp. Univ. of Calif., Berkeley, Calif: Lawrence Berkeley Laboratory. (One of four volumes on the same subject. Subsequent volumes are numbered as Vols. II, III, and IV of the same basic publication).

(a) They are almost here; see the final chapter.

OUTLINE **THE EARLY DAYS OF** **MANMADE RADIOISOTOPES**

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1. The first part of the document discusses the importance of maintaining accurate records of all transactions. It emphasizes that proper record-keeping is essential for the integrity of the financial system and for the ability to detect and prevent fraud.

2. The second part of the document outlines the specific procedures for recording transactions. It details the steps involved in the accounting cycle, from identifying the transaction to posting it to the appropriate ledger account.

3. The third part of the document discusses the importance of internal controls. It explains how internal controls can be designed to prevent errors and fraud, and how they can be used to ensure the accuracy of the financial statements.

4. The fourth part of the document discusses the importance of auditing. It explains the role of the auditor in verifying the accuracy of the financial statements and in detecting any errors or fraud.

5. The fifth part of the document discusses the importance of the Sarbanes-Oxley Act. It explains how this act has changed the way that companies report their financial information and how it has increased the accountability of corporate executives.

6. The sixth part of the document discusses the importance of the Generally Accepted Accounting Principles (GAAP). It explains how these principles provide a common framework for the preparation of financial statements and how they are used by investors and other stakeholders to make decisions.

Capsule Chronology^(a)

- 1919** First artificial transformation of an element; alpha particle on nitrogen (Rutherford).
- 1930–1932** Invention of cyclotron (E. O. Lawrence and M. S. Livingston at Berkeley). Plans outlined in 1930. Paper sent to press in 1931, published in 1932.
- 1931** Van de Graaff electrostatic generator constructed.
Linear accelerator constructed (Sloan and Lawrence at Berkeley).
- 1934** First artificially produced radionuclide (Irène Curie and J. F. Joliot, Paris).
Realization that cyclotron at Berkeley could be used for production of radioisotopes useful for tracer chemistry and biomedicine (Henderson, Livingston, and E. O. Lawrence).
Production and use of radiosodium. Prophetic to nuclear medicine (Hamilton and Stone at Berkeley).
- 1934–1946** Cyclotron and other accelerators produce hundreds of radionuclides of use in biology and medicine.
- 1935** Hevesy publishes on uses of radioisotopes in biology (Copenhagen).
Lawrence uses ^{24}Na as a tracer (Berkeley).
- 1936** First use of ^{32}P in therapy (John Lawrence, Berkeley). Produced in 37-in. cyclotron. Also prophetic to nuclear medicine.
- 1936–1940** Use of radioiodine from MIT^(b) cyclotron. Patients at MGH (Evans et al.). Animals at MIT (Hertz, Roberts, and Evans).
Tracers demonstrate the dynamic state of body constituents.
- 1937 et seq.** Radioiodine used for diagnosis and therapy (Hamilton and E. O. Lawrence at Berkeley).
Use of radiosodium in humans grows.
- 1937–1939** Seaborg and colleagues produce and isolate many radionuclides of importance to biology and medicine using Berkeley cyclotrons, mostly the 37-in. machine.
- 1938** Radioiron revolutionizes ideas about iron metabolism (Hahn, Bale, Lawrence, and Whipple at Rochester).
Rochester cyclotron produces many other isotopes for biomedical use.
Electron-capture radionuclides discovered (Alvarez at Berkeley). Much use in biomedicine because of low dose delivered.
- 1938 et seq.** All physics work at Berkeley's 37-in. cyclotron suspended for one full day each week to allow treatment of cancer patients with neutrons.

(a) This considers primarily the decade from 1932 to 1941.

(b) For abbreviations and acronyms, see Appendix D.

1939 The 60-in. cyclotron at Crocker Laboratory, Berkeley, goes into operation and is designated a "medical cyclotron."

Kamen and colleagues use ^{11}C extensively in biochemistry.

1940 Kamen produces and uses ^{14}C .

1941-1946 Phosphorus-32 and other radionuclides obtained from a growing number of accelerators (Ohio State; Washington U., St. Louis; etc.).

Chapter 5

The Early Days of Manmade Radioisotopes

Overview

This short chapter provides a bridge between the first major section of the book, "The Naturally Occurring Radioisotopes," and the second, "Manmade Radioisotopes." It provides a brief summary of the first years of manmade radioisotopes and their significance to biomedical science. While nominally it concentrates on the decade of the 1930s, which includes some years prior to the announcement of the first artificial production of a radioisotope in 1934, it also reaches back into the 1920s when the first tracer experiments were done. It includes a few events that came to fruition in the 1940s.

The discussion is aimed primarily at establishing the setting in which the intensive researches on the biomedical behavior of radioisotopes were carried out during World War II. The era marked fundamental changes in our concepts of life processes. Only relatively broad concepts are described. The literature citations are sparse and consist mostly of citations of unusual historical importance or illustrations of points under discussion. A few general references are given to pertinent monographs and texts. Most of these were written in later years, but they include substantial summaries of the period of interest.

The final section takes up the bearing of the work of this era on our primary focus. Actually, there was little formal work on the toxicology of the new manmade radioisotopes except as an adjunct to isotope therapy. Nevertheless, essential techniques and instrumentation were developed and some preliminary ideas formulated that were essential to the more overt biomedical investigations in later decades. These are considered briefly.

There are also a few speculations on the possible presence of untoward effects in man during these years of rapid development of a new and initially esoteric tool.

I. Introduction

With this chapter, we begin the subject that will occupy our attention through most of the balance of this book: the behavior and effects of manmade radioisotopes in living organisms. By the "early days" we mean primarily the decade

of the 1930s. This was a remarkable decade in nuclear physics and marked the final transition from classical to modern eras. Included was, of course, the development of several kinds of high-voltage machines for accelerating particles to impinge upon a target. Of special importance to biomedical science was the invention of the cyclotron (Lawrence and Livingston 1932).

The field of tracer chemistry, i.e., the use of tagged atoms as tracers for the behavior of a stable element or as a marker for biochemical reactions, came into its own during this decade. Also, nuclear medicine, which is a direct descendant of tracer chemistry, began, although not with that name. By the end of the 1930s, a relatively rare technique and something of a curiosity had become a commonplace tool in much of biomedicine. The changes in biomedical science were indeed almost as dramatic as those in nuclear physics, albeit accompanied by less fanfare.

A book devoted to milestones in understanding the health effects of radioisotopes cannot neglect discussing this era, even though the concerns for effects were not nearly as strong as in following decades. Since ample reviews of the details of this era are legion, the coverage here will be primarily for historical perspective. Only a few direct literature citations will be made, since, on the whole, this is not the place to discuss the research results. There is a general bibliography at the end of the chapter, which gives some of the key monographs and texts pertinent to the era.

II. Preparing the Way

The method of radioactive indicators began well before manmade radioisotopes were available. The idea that isotopes could exist was accepted in the early 1900s. Rutherford observed in 1919 that bombardment of the nitrogen atom by alpha particles from natural sources resulted in production of an isotope of oxygen.^(a) Hevesy and Paneth collaboratively used radium-D^(b) (^{210}Pb) as a tracer for the behavior of a stable element, lead, in inorganic reactions as early as 1913 (Paneth and Hevesy 1913; Hevesy and Paneth 1938). Hevesy entered the biomedical field with a study of the absorption and translocation of lead by plants, viz., bean roots (Hevesy 1923). In both cases, it was a most ingenious conversion of failure in one enterprise (separating radium-D from "all that nuisance lead," impossible because radium-D was an isotope of lead) into glowing success in another (the tracing of a stable element by one of its radioactive isotopes). Very soon, Hevesy published (with collaborators) the first experiments on animals. These used radium-E, which is a 5.0-day-half-life isotope of bismuth (^{210}Bi). Lead-210 (thorium-B), already used in the bean root experiments, was also tried in animals.

Many other tracer experiments followed as described in detail in the informative two-volume collection of Hevesy's papers (Hevesy 1962) and in the many tracer chemistry compendia listed at the end of this chapter.

(a) It became clear that the old dreams of the alchemists to transform "base metals into gold" had been unrealized because a nuclear reaction is required. Only when the strong electrostatic repulsion of the charged nuclei in atoms is overcome can nuclear reactions occur. This requires the high initial velocity seen only with high-energy ionizing radiations, and these do not occur in ordinary chemical reactions.

(b) For convenience in reading the early literature, the now obsolete terminology (radium-D, etc.) is used temporarily.

At Harvard, Herman L. Blumgart and colleagues used solutions of radium-C (^{214}Bi) in the late 1920s for injection into humans (Blumgart and Yens 1927; Blumgart and Weiss 1927). Their aim was to study the velocity of the circulation, which they did by injecting the ^{214}Bi solutions into one arm and detecting the appearance of the energetic gamma rays in the other. Their detection device was nothing other than a modified Wilson Cloud Chamber placed on the un-injected arm. (It was later replaced by an early type of Geiger counter.) The usual arm-to-arm circulation time was eighteen seconds. This general method using naturally occurring gamma-emitting isotopes was expanded to measurements of pulmonary circulation time, blood volume, and many other physiological processes. (More in chapter 20.)

There were a few tracer experiments done using ^{226}Ra and ^{222}Rn . This latter was also pioneered by Blumgart and, according to Shields Warren (Warren 1978), may have preceded the use of radium-C and thus been the very first use of an isotopic tracer for a physiological measurement in man. But the detection of alpha particles posed much greater problems than the gamma rays from substances like ^{214}Bi . Fortunately, relatively few such experiments were carried out in humans. From what we now know, such use of alpha-particle emitters would have been hazardous.

These works established the basic methodology of tracer chemistry for use both in vivo and in chemical systems in vitro.

In the early 1930s, Urey separated deuterium from hydrogen. This had two especially important results. The use of stable isomers as tracers for their more abundant companions began in earnest. Later, the nucleus of deuterium was to become a most useful projectile for accelerators. The mass spectrograph assumed an important role as another tool for the method of tracer chemistry, and some important findings regarding the dynamic state of body constituents resulted.

III. Manmade Radioisotopes Enter the Picture

The first production of a new radioisotope by the deliberate transmutation of another element through the ingenuity of man is attributed to Irène Curie and her husband Jean Frédéric Joliot.^(a) They had been bombarding various light metals with alpha particles from ^{210}Po . Emission of neutrons, protons, and positrons ($+1e$) resulted from such bombardment. The key observation was that, while the neutron and proton emissions ceased, the positron emission *did not* cease after cessation of the bombardment. It continued with an activity that decayed away exponentially with time as for an *ordinary radioelement*. The phenomenon was seen with several light metals. The products were all new radioelements, and they had been formed *de novo* in the experiment. In the case of boron, the result was ^{13}N . In the case of aluminum, the result was ^{30}P . With magnesium, the product was ^{27}Si .

Having already seen the ease with which credit for a new discovery can travel away from its rightful recipient, Irène and her husband got off a quick note to *Nature*, which was published in the February 10, 1934, issue (Joliot and Curie 1934). The first production of a new radioisotope by man had been

(a) The reader will remember that we forgave the delay caused by Irène's gestational period in her mother's isolation of radium because she was later to do something big in her own right (cf chapter 1).

accomplished, a process markedly in contrast to the separation of constituent elements from naturally occurring mixtures.

Within a month of the Joliot-Curie announcement, the Berkeley group announced the use of both deuterons and protons in the cyclotron to bombard a variety of elements between lithium and chlorine. Every target was observed to emit both gamma radiation and ionizing particles (positrons) for some time after bombardment ceased. The activity fell off exponentially with time and was characteristic for each target element. The paper was done by Henderson, Livingston, and Ernest Lawrence and appeared in the *Physical Review* for March 15, 1934.^(a)

In this case, the source of the bombarding particles was a machine invented and made by man. Its capacity to produce new radioisotopes exceeded by far that of even the most powerful source of natural alpha particles. The age of artificial radioisotopes was under way in earnest. Tracer chemistry rapidly took over much of biochemistry, some of physiology (e.g., Hamilton and Stone 1937), and bits and pieces of medicine.

Developments succeeded each other in close succession. Radioisotopes of the physiologically important elements such as sodium, potassium, chlorine, bromine, iron, phosphorus, and iodine were given to both humans and animals. A popular technique in man was to place one hand within a box with a thick lead shield and grasp a counter tube. This tube could register the appearance of these entities as a function of time after entrance to the body via the digestive tract. It became clear that sodium was much more mobile than potassium and that potassium was largely bottled up inside cells. Excretion of the radioelements was determined both in the normal human and in patients with various diseases.

Especially useful and popular isotopes in this era were ^{24}Na ; ^{42}K ; ^{128}I , followed in time by ^{130}I , and later still ^{131}I (^{125}I did not enter until 1946); ^{32}P ; several isotopes of sulfur, the most useful being ^{35}S , which is now produced in a nuclear reactor; isotopes of chlorine; and several isotopes of iron, primarily ^{59}Fe and ^{55}Fe . Most of the tracer work involving reactions of hydrogen involved heavy hydrogen (deuterium), since the existence of tritium, the radioactive isotope, was not demonstrated until 1939.

Experiments in the tracer realm with these demonstrated strikingly what Hevesy called in his Nobel Prize lecture "the dynamic state of body constituents," i.e., the molecules building the organism are incessantly renewed. Perhaps most surprising was the rate of turnover of atoms and molecules in bone, formerly considered a more or less static structure. Also, the work with isotopes of iron completely revolutionized ideas concerning iron metabolism and its role in the body economy (Hahn et al. 1938). This included both the realization that iron in certain vital molecules is jealously guarded against deficiency of intake and that iron is absorbed from the gastrointestinal tract only as it is needed to maintain the stores at optimum levels.

With the addition of radiocarbon to the roster of radioisotopes (first the short-lived ^{11}C and later the long-lived ^{14}C) by Kamen, entrée was obtained to both the bicarbonate- CO_2 cycle and the vast domain of organic compounds in biochemical reactions. Classic experiments using radiocarbon, such as the early

(a) Without doubt, the phenomenon had been occurring all along in accelerator targets, but the after-decay was not focused upon until the Joliot-Curie announcement drew the attention of the Berkeley workers.

ones at Harvard on glycogen synthesis and the work on photosynthesis at Berkeley, brought about radical revisions concerning our ideas of the mobility, transfer, and synthesis of carbon compounds of biochemical importance.

The cyclotrons at Berkeley were unabashedly devoted to biomedical work. This was in part because Ernest Lawrence had always had an interest in medicine, and his brother John, a physician, was close by to help with biomedical details and the selection of important problems to study. Such collaboration was not limited to Berkeley, however. There were cyclotrons at Harvard-Massachusetts Institute of Technology (MIT), Rochester, and Washington University, all devoted to a significant extent to the preparation of radioisotopes for biomedical work. In fact, for nearly all, the base for supporting funds was partly the promise of their products to biological and medical research and therapy.

One of the most completely developed histories of the role of collaborative efforts of workers from many disciplines is seen in the organization and construction of the joint MIT-Harvard cyclotron as described by Robley Evans in a review published much later (Evans 1975; also Brucer 1978). The *raison d'être* was entirely medical, and the first (by a short time) administration of radioiodine (the short-lived ^{128}I) to a patient came as a result of this effort. Soon, radioiodine was being used in several places. Among these was Berkeley, where Joseph Hamilton, a young physician (originally a psychiatrist but also a first-class chemist), worked under the stimulation of both John and Ernest Lawrence. We will have many occasions to consider other aspects of Hamilton's work in later contexts.

Tracer chemistry was not the only goal in these works. Besides the obvious physical experiments, the Lawrence brothers, for example, had therapeutic uses as a primary objective in building their machines. Indeed the largest cyclotron of the decade, the 60-in. machine at the Crocker Laboratory, was called "The Medical Cyclotron" (Lawrence 1939).

Therapeutic amounts of several radioelements were indeed made and used, some of them before (and during) World War II (Evans 1975; Brucer 1978). Radiosodium (^{24}Na) was tried at Berkeley to deliver the equivalent of whole-body external radiation in the treatment of leukemia. Radiophosphorus (^{32}P) was applied in several centers both in the United States and abroad (especially in Hevesy's laboratory) for the treatment of blood disorders. The first therapeutic use of ^{32}P appears to have been by John Lawrence on Christmas Eve of 1936. Phosphorus-32 eventually became the treatment of choice for polycythemia vera, and hopes were high for its effectiveness in the treatment of some forms of leukemia. (More about this will appear in the chapter on nuclear medicine.)

To bring about these accomplishments, much individual labor and experimental insight were needed. A decent tracer experiment or preparation of an isotope for therapeutic administration required team efforts and group spirit. Many of the early isotopes of greatest interest had relatively short half-lives. Progression from removal of the target to final counting had to be accomplished with dispatch. Organization of the many steps resembled a military operation. Chemical separations were necessarily by the classic methods. (Ion exchange methods had not yet come on the scene.) The early steps required considerable shielding against radiation and help from the cyclotron crew. The later steps required decisions on whether to measure the activity of the product in a solid or gaseous form and in what chemical compound. Nearly all variations were tried. While the tedious final counting beat endless titrations, many technicians had to be consigned to long days of work at the manually operated and

somewhat temperamental devices for counting radioactivity. Comparison to standards had to be rigorous and frequent.

There were pitfalls too. Rigorous criteria of isotopic purity were required. One had to be certain that the tracers were not wandering from one moiety to another without the knowledge of the experimenter. With the very small amounts involved, the chance that the tracer was attached to an impurity rather than the substance under study had to be guarded against. The phenomena of low concentration chemistry were, of course, inevitably involved, while, especially at higher concentrations, the production of radiocolloids had to be reckoned with. Many practical solutions were put together from necessity; and these persisted into other areas such as radioisotope toxicology. As Martin Kamen warned, bad chemistry is still bad chemistry, even with the convenience of a handy tracer atom. Perhaps it was even more likely to occur because the low concentrations precluded some of the classic tests of purity. But on the whole, the active participation of physical scientists in the teams made the errors less numerous than they otherwise might have been.

A further example of fruitful collaboration among physics, chemistry, and medicine is seen in the genesis of more or less pure ^{131}I . The short half-life of ^{128}I (twenty-five minutes) was a nuisance for both producer and user. The anecdote concerning its isolation^(a) has appeared in several places. We will quote the text used by Brucer (1978). The principals are Joseph Hamilton and Glenn Seaborg at Berkeley in 1938.

Unaware that a 13-day iodine had been announced in February, one day in the spring of 1938 Hamilton ran into Glenn Seaborg on the steps of Le Conte Hall (the physics building at Berkeley). Seaborg was the chemist who prepared the pure radioisotopes from irradiated cyclotron targets. Hamilton complained bitterly about the 25-minute half-life of I-128; "Why can't you make me an iodine isotope with a longer half-life?"

"We can," said Seaborg. "How long a half-life do you want?"

"Oh, about a week."

Seaborg and his physicist partner, Jack Livingood, prepared some tellurium targets. They bombarded the targets in the 37-inch cyclotron with 8-MeV deuterons. Chemical separation and identification procedures were carried out while wearing gas masks to ward off the dreaded "tellurium breath." In a week Seaborg delivered the first and only radioisotope ever discovered to fill a physician's prescription, a sample of a new 8-day iodine-131 with the comment, "If you don't like what we're making we'll discover something else."

Brucer comments further:

I-131 was a significant achievement, not because it later became top-dog in Nuclear Medicine, but because it opened up the possibility that alternate choices of nuclides possibly meant a choice of dosages—maybe even therapy could be considered. (Brucer, 1978)

The publication reported both a twelve-hour ^{130}I and the eight-day ^{131}I (Livingood and Seaborg, 1938).

There was tedium also in the cyclotron operations. Irradiation times sometimes had to be quite long, especially to prepare the quantities of isotope needed for therapeutic trials. Physicists whose main research interests were in

(a) The possibility of longer-lived iodines was recognized in the mixtures in 1937 by letting them "age" and the ^{128}I , for example, decay out.

other directions developed almost saintly patience during these long sessions, based in general on their personal conviction of the importance of the biomedical work. One of these was Arthur Roberts, a member of the MIT-Harvard team that first reported the uptake of radioiodine as a measure of thyroid function in rabbits (Hertz, Roberts, and Evans 1938). At a much later time, probably the fall of 1942 (Evans 1981), Roberts produced a somewhat wistful ditty around the long hours of cyclotron irradiation times entitled, "The Cyclotronist's Nightmare or Eight Millicuries by Half-Past Nine." The first verse reads:

Once upon a midnight dreary
The cyclotron crew was weak and weary;
In walked the Boss with a smile so cheery,
In walked the Boss with a very broad smile.
"Boys" he said, "Here's a wonderful chance"
"Boys" he said, "It'll make you want to dance"
"Boys" he said, "We must activate some iron"
"Eighty millicuries by half-past nine."^(a)

We will have reason to return to this text in another connection in section IV.

There is no doubt that these new methodologies added an entirely new dimension to biology and medicine. In addition to the research findings themselves, the close collaboration of scientists from many disciplines was an essential ingredient. In retrospect, it was in basic biochemistry and physiology that the quantum jumps were made. Therapy was intriguing and stirred much enthusiasm but was not so obviously a new dimension.

The meaning of the 1930-1940 development of tracer chemistry and the preludes to nuclear medicine to our subject of possible health effects is not as direct as in later years. But it was very real, as we shall see in the next section.

IV. Overtones for Radiation Toxicology

During the decade of the 1930s, excitement ran very high for exploring the new vistas opened by the availability of radioisotopes. Possible untoward effects of these new entities were undoubtedly frequently either not considered at all or brushed aside as minimal.^(b) The painful saga of the radium dial painters, chemists, and patients was slow to cross the boundaries into conventional physiology, biochemistry, and medicine, which were undergoing a quiet revolution, as the tracers demolished one old idea after another. Quite obviously, the highly radioactive targets, i.e., the source material, required considerable shielding and special techniques. The early radiation protection experts were quite aware of the potential hazards of radioisotopes in the body, as well as their potential as sources of external radiation, and let their thoughts be known. But once the "hot" sources were diluted to tracer levels, worries over toxic effects were minimal. On the whole, this sanguine attitude was probably justified for tracer applications.

(a) Excerpted from copy kindly supplied by Robley D. Evans (1981) who was "The Boss" in this not so fictitious composition.

(b) By contrast, there was immediate and substantial interest in possible toxicity of heavy hydrogen (deuterium) as soon as it was separated in quantity. Indeed, some effects were found.

1. The amounts of radioisotope used were necessarily small because the amounts available from the accelerators were small in an absolute sense.
2. The half-lives of the more commonly used materials were relatively short.
3. The investigators were sufficiently aware of the biological effects of radiation to make every effort to be sure the radiation doses from the tracers did not alter the processes under study.
4. The equipment of even this early decade was sufficiently sensitive to respond to very small quantities of radioactive materials. Contamination of laboratory and equipment had to be scrupulously avoided. Thus, the needs of the experiments brought with them a considerable measure of safety.

There had to be some careless workers and some laboratories where potential health hazards were pooh-poohed. Fortunately, the nature of the isotopes and the small quantities involved made it unlikely that tracer-chemistry experiments per se were responsible for demonstrable health effects. It was the personnel manning the accelerators who were vulnerable and who died later of leukemia or developed cataracts from the practice of lining up the cyclotron beam by eye. We cannot be sure, but it seems likely that external radiation from the beam and scatter played a more important rôle in these deaths than radioisotope ingestion or inhalation.

The situation was somewhat different in the realm of planned therapeutic administration to humans. The dial-painter story had alerted some segments of the medical profession and, even then, a vocal segment of the public and the press. John Lawrence tells in an after-dinner address given at the second annual meeting of the then-new Society of Nuclear Medicine (Lawrence 1956, extracted and published in 1979 in the *Journal of Nuclear Medicine*) of the suspicion directed toward those members of the medical profession who gave demonstrations on the creamed-chicken circuit by swallowing a small amount of radioiodine or radiosodium, or did a tracer experiment with an animal or plant. The idea that application of artificial radioactivity to humans would amplify alarmingly the tragedies seen in the dial painters was raised clangorously in some quarters. The large difference in biological effectiveness of the beta and beta-gamma emitters compared to alpha emitters like radium, the effect of the much shorter half-lives and deposition in general in soft tissue rather than bone were not grasped by those alleging that the radium saga was being extended to new, unsuspecting recipients.

On the other side of the coin, there is no doubt that some of the practices and some of the doses would not pass muster today. The investigators had a strong (and understandable) tendency to use themselves as guinea pigs for new isotopes and new ideas. Recommendations for permissible dose were more lenient than they are now. We cannot point to any specific instances of proven damage to investigators or patients from the use in humans of therapeutic doses of artificially produced radioisotopes in the 1930s. But neither can we be sure that there were none. The number of individuals involved was far too small to permit an acceptable retrospective epidemiologic study. Hence, we will probably never know the extent of the toxicological effects of therapeutic levels of radioisotopes used in that decade. It is unlikely that the number is zero.^(a)

(a) Clearly some of the early patients were alive and well in the 1950s, and a few remain today who would probably have died of their malady had they not been treated. Thus, even if there were risks there were also benefits.

The composition by Arthur Roberts quoted in the previous section has as a subtle theme in a later refrain the possible confusion of units; the prescription called for *milligrams* not *millicuries*. Here in jocular song and verse is one of the nightmares of dosimetry, the misread unit or the misplaced decimal point. That such mistakes have been made, albeit very infrequently, is part of the folklore of nuclear medicine, as of all of drug therapy. Deleterious effects no doubt resulted from these. But it is not our function here to attempt to document these rare instances, except to say that, in general, they were less likely to happen with the new radioisotopes than with conventional drugs. The low frequency of use in the decade of the 1930s would alone preclude there being many instances. Nevertheless, in reviewing the overtones for toxicology of the decade of the 1930s, we must note such possibilities.

A sidelight on considerations of toxicity in this period lies in a story told by John Lawrence at the Society of Nuclear Medicine meeting already cited. There was much interest in the biological effectiveness of the neutrons from the cyclotron. Paul Aebersold, whom we will meet in later chapters, was a graduate student at Berkeley at the time. He fashioned a small chamber that would hold a rat and that could be placed near one of the Dees within the cyclotron. The machine was turned on for *three minutes*. The crew then crawled into the space to retrieve the animal. The rat was dead. This caused considerable alarm and, according to Lawrence, instilled great respect for the biological potential of these new radiations. This respect lasted, and it undoubtedly prevented some rash and dangerous short cuts in cyclotron operations. It was not until twenty years later that Lawrence admitted that the histologic sections from that rat showed that it had died of suffocation (Lawrence 1956, 1979).

The uses of radioisotopes in these early years made many contributions to radioisotope toxicology as we now know it. These included:

1. development of instrumentation
2. development of methodologies for preparation and handling of radioisotopes
3. development of calculations for the estimation of dose from both the tracer and therapeutic levels, especially the latter
4. development of standards for worker exposure
5. characterization of the pharmacokinetics (i.e., the location and translocation) of the principal radioisotopes. (Of special importance was the uptake in the organ of interest relative to other tissues or the whole body.)
6. preliminary characterization of the effects of beta and beta-gamma emitters
7. synthesis of and behavior of a wide variety of compounds containing radioisotopes
8. effects of disease states on the behavior of radioactive elements alone or in specific compounds.

Let us consider a few of these in more detail.

The methodologies developed for preparing and handling radioisotopes for tracer experiments or for therapy were essentially the base line for the work of the following decade (chapter 6), except for alpha-emitter detection and measurement. Alpha emitters were already in the domain of radiation toxicology by virtue of the work with radium. Radiation doses were estimated rather crudely, primarily on the basis of energy and half-lives. The rad unit had not been proposed. The complex internal dosimetry of the next decade was still to come. But empirical determination of no-effect levels was engaged in frequently. In the

case of tracer chemistry, radiation effects could not be allowed to complicate the basic processes under study. For therapy, concentrations had to be effective to the target tissue without undue damage to normal tissues. By virtue of constant testing, the dose of ^{32}P , for example, which would be effective against polycythemia vera, yet would not produce unacceptable damage to other bone marrow cells, was worked out as best it could be. Individual variations in response and apparent sensitivity were large, however. As a result, questions of dose fell to some extent in the area of that sixth sense that therapists should have—clinical judgment.

Probably one of the most concrete legacies of this first decade of manmade radioisotopes to future work was in the characterization of the behavior of isotopes in the body. This was not overt. It was simply a coincidence in that the same kind of information was needed for both fields.

For reasons that are not entirely clear, radiation toxicology has made little use of the knowledge gained concerning the effects of disease states on the behavior of radioisotopes. Probably the focus has been so concentrated on toxic effects in normal organisms that the influence of pathological states has not been considered very important. Only in nuclear medicine do the possibilities of altered metabolism by virtue of the underlying disease state become a commonplace item to consider. Yet, as radiation protection extends beyond the normal worker, these considerations may become critical. Unfortunately, the literature on such influences, even for the first decade, is widely scattered and in need of review and compilation.

In toto, the interrelationships of the work in tracer chemistry during the first decade of manmade radioisotopes, the therapeutic uses, and our field of radiation effects are very loose and for the most part unplanned. The fact that both depend upon the same body of knowledge is their most tangible interrelation. The stage was being set for the intensive research to follow in and after World War II. We will consider these in chapters 6 and 7.

V. Summary and Commentary

There can be no doubt that the groundwork for tracer chemistry, nuclear medicine, and radionuclide toxicology was laid in the decades of the 1920s and 1930s. It started with the use of naturally occurring radionuclides as tracers; it received a considerable advance by the production of manmade radionuclides by Irène Curie and her husband, F. Joliot, in 1934; and a quantum jump made possible by the invention of various accelerators by the physicists. The cyclotrons at Berkeley were soon followed by machines at MIT, Washington University in St. Louis, the University of Rochester, and elsewhere. It was an era of close collaboration among physicists, chemists, and biomedical personnel. The short half-life of most of the radionuclides required real team work.

There was about an equal mix in the earlier periods of work aimed at biochemical and physiological mechanisms using tracers, applications to understanding of disease processes (especially the thyroid [^{131}I] and certain blood disorders [^{32}P]), and forays into frank therapy. Gradually, some separation of the lines of investigation began. It probably would have gone further, but the prodromal needs of the war effort interfered. Many of the principal investigators of the decades considered in this chapter became key individuals in the efforts to come in World War II.

Although our treatment is brief, it should be apparent that this period meant much for the future of all of biomedical science, both "pure" and "applied." If we compare the number of lives saved or made more comfortable by the products of these decades, as later applied, with the deleterious effects, even fatalities, occurring to date, we must conclude that these developments have had a positive impact overall.

References

- Blumgart, H. L. and S. Weiss. 1927. Studies on the velocity of blood flow. II. The velocity of blood flow in normal resting individuals, and a critique of the method used. *J. Clin. Invest.* 4:15-31.
- Blumgart, H. L. and O. C. Yens. 1927. Studies on the velocity of blood flow. I. The method utilized. *J. Clin. Invest.* 4:1-13.
- Brucer, M. 1978. The genesis of thyroid-radioiodine or how Robley Evans became a super-salesman before he had a product to sell. In *Vignettes in nuclear medicine*, no. 90. St. Louis: Mallinckrodt.
- Evans, R. D. 1975. Early history (1936-1946) of nuclear medicine in thyroid studies at Massachusetts General Hospital. *Med. Phys.* 2:105-09.
- Evans, R. D. 1981. Letter dated July 10, 1981.
- Hahn, P. F., W. F. Bale, E. O. Lawrence, and G. H. Whipple. 1938. Radioactive iron and its metabolism in anemia. *J. Am. Med. Assoc.* 111:2285-86. (Also 1939, *J. Exp. Med.* 69:739-53.)
- Hamilton, J. G. and R. S. Stone. 1937. The intravenous and intraduodenal administration of radio-sodium. *Radiology* 28:178-88.
- Henderson, M. C., M. S. Livingston, and E. O. Lawrence. 1934. Artificial radioactivity produced by deuteron bombardment. *Phys. Rev.* 45:428-29.
- Hertz, S., A. Roberts, and R. D. Evans. 1938. Radioactive iodine as an indicator in the study of thyroid physiology. *Proc. Soc. Exp. Biol. Med.* 38:510-13.
- Hevesy, G. 1923. The absorption and translocation of lead by plants: A contribution to the application of the method of radioactive indicators in the investigation of the change of substance in plants. *Biochem. J.* 17:439-45.
- Hevesy, G. 1962. *Adventures in radioisotope research*. New York: Pergamon Press.
- Hevesy, G. and F. Paneth. 1938. *A manual of radioactivity*. 2d ed. London: Oxford University Press.
- Joliot, F. and I. Curie. 1934. Artificial production of a new kind of radio-element. *Nature* 133:201-02.
- Lawrence, E. O. 1939. The medical cyclotron of the William H. Crocker Radiation Laboratory. *Science* 90:407-08.
- Lawrence, E. O. and M. S. Livingston. 1932. The production of high speed light ions without the use of high voltages. *Phys. Rev.* 40:19-35.
- Lawrence, J. H. 1956. Early experiences in nuclear medicine. *Northwest Med.* 55: 527-33.
- Lawrence, J. H. 1979. Early experiences in nuclear medicine. *J. Nucl. Med.* 20: 561-64.
- Livingood, J. J. and G. T. Seaborg. 1938. Radioactive iodine isotopes. *Phys. Rev.* 53:1015.
- Paneth, F. and G. Hevesy. 1913. Über Radioelemente als Indikatoren in der analytischen Chemie. *Monatsh. Chem.* 34:1401-07.
- Warren, S. 1978. Personal interview, May 19, 1978.

General References

- Clark, H. T., ed. 1949. *Symposium on the use of isotopes in biology and medicine*. Madison, Wisc.: Univ. of Wisc. Press.
- Comar, C. L. 1955. *Radioisotopes in biology and agriculture*. New York: McGraw-Hill.

- Glasstone, S. 1950. *Sourcebook on atomic energy*, chapters 9, 10, and 16. New York: D. Van Nostrand.
- Hevesy, G. 1948. *Radioactive indicators*. New York: Interscience.
- Kamen, M. D. *Isotopic tracers in biology—An introduction to tracer methodology*. New York: Academic Press. [There are several editions. The one in 1947 has a detailed chapter on ^{11}C , which was omitted later because of the greater convenience of ^{14}C . Since ^{11}C is now back in use, the interested reader may wish to seek out this early edition. The third edition was published in 1957 and had four printings, the last in 1965.]
- Kamen, M., ed. 1948. *Symposium on preparation and measurement of isotopes for use in biochemistry*. Presented at the 112th meeting of the American Chemical Society held in New York, September 15-19, 1947. Naval Medical Bulletin, supplement to vol. 48. [Note: This symposium brought together a large number of those who had been working in tracer chemistry before or during World War II. It was one of the first opportunities many of them had to describe the developments of the 1941-1947 period and is well worth the trouble to find.]
- Kimball, A. H. 1949. *Bibliography of research on heavy hydrogen compounds*. New York: McGraw-Hill.
- Lawrence, J. H. and J. G. Hamilton, eds. 1948. *Advances in biological and medical physics*, vol. 1. New York: Academic Press.
- Massachusetts Institute of Technology. 1940. Conference on Applied Nuclear Physics held at Cambridge, Mass., October 28-November 2, 1940. Abstracts in *J. Appl. Phys.* 12(1941):296-350. [Note: This conference was a rare occasion at which the many aspects of applied nuclear physics and chemistry, as they stood just before World War II, were discussed together. The subjects included geology and geophysical applications of nuclear physics; metallurgy; tracer techniques in general chemistry, in analytical chemistry, and chemical effects of nuclear transitions; tracers in studies of animal metabolism, biochemistry, and plant metabolism; cancer therapy; radium and roentgen therapy; neutron and artificial radioactivity therapy; dosage measurements; radiobiology; isotope production and separation; radiation measurements; and worker protection. The author index provides as close to a complete roster of the best known contemporary American investigators in the field as can be found.]
- Schoenheimer, R. 1946. *The dynamic state of body constituents*. Cambridge, Mass.: Harvard Univ. Press.
- Siri, W. E. 1949. *Isotopic tracers and nuclear radiation*. New York: McGraw-Hill.

OUTLINE

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Capsule Chronology

- 1939 Correct description of phenomena of nuclear fission (Meitner and Frisch, Germany).
- 1941 Pecher (Berkeley) finds that radiostrontium behaves like calcium and deposits in bone.
- 1942 The chain-reacting pile works. Large quantities of fission products expected.
- 1942-1943 Concern develops at Metallurgical Laboratory (Chicago) about potential hazards of radioxenon, and soon thereafter, of ^{131}I and fission products.
- 1942-1945 Concern over possible use of fission products in radiological warfare leads to Projects Peppermint and Gabriel.
- 1942-1947 Systematic study of fission products at Berkeley (Hamilton, Axelrod, Copp, Lanz, Scott, et al.). Radionuclides produced in 37-in. or 60-in. cyclotron. All work at tracer level because of small quantities. Parenteral, ingestion, and intratracheal routes of administration used.
- 1943-1945 Berkeley classified reports show tissue distribution, retention, and elimination kinetics.
- 1944 Substantial group begins work at Met Lab (Chicago) on biomedical aspects of fission products. Emphasis on effects, as well as metabolism. Some of the work done at Clinton Labs.
Special tools developed.
- 1945 Summary project reports from Berkeley. Each element seems to have its own behavior.
- 1945 et seq. Much work at Chicago (Schubert et al.) on radiocolloids and chemistry of fission products pertinent to biomedical problems.
- 1946 Barium-lanthanum couplet investigated in animals at Met Lab (R. Finkle and Snyder). Growth, development, hematological effects, LD_{50} .
- 1946 Fission products investigated as carcinogenic agents at Chicago (Lisco, M. Finkel, and Brues; also Prosser). Beginning of large experiment with mice. Carcinogenicity to bone demonstrated.
- 1947 Metabolism and effects of strontium investigated at Met Lab, Chicago (Anthony et al.).
Phosphorus-32 used for comparison and as base line for less well-known elements such as cerium.
Oral ^{91}Y produces carcinoma of the colon in rats (Grundhauser, Met Lab).
Transmission of fission products from mother to fetus studied at Chicago (M. Finkel). Included deposition in fetus.
Fission product studies with dogs using ^{89}Sr and ^{90}Sr begin at Chicago (Swift and Prosser). LD_{50} determined, as well as metabolism and hematology. First work with large animals.
Fission products studied in goldfish at Chicago (Prosser et al.).

Very complete reports from Berkeley on metabolism of strontium, barium, yttrium, cerium, praseodymium, zirconium, ruthenium, tellurium, iodine, xenon, cesium, and "fission product mixture." In general, gut absorption poor. Liver takes up considerable amounts early, but they soon leave and are either excreted or go to bone. Bone retention is quite long. Ruthenium, tellurium, cesium, and xenon do not localize in bone. Autoradiography shows considerable differences in microscopic distribution of different fission products in bone. Strontium is most like calcium.

1949 Open literature reviews of Berkeley work.

Ion distribution studied in plants (Jacobson and Overstreet at Berkeley).

Part of the Met Lab work reaches open literature, but much remains unpublished.

EARLY POSTWAR YEARS

Berkeley: Old 37-in. cyclotron disappears along with its building (the old "Radiation Laboratory"). Crocker Laboratory dismantled but 60-in. cyclotron goes (in pieces) to the University of California, Davis. Much activity in teaching about the new science of radioactivity.

Chicago: Large experiment continues on long-term effects and relative toxicities in mice.

Hanford: Biology work begins; includes iodine in sheep.

Chapter 6

New Dimension Number One— The Fission Products; 1939–1950

Overview

This chapter concentrates on what the biomedical community did to react to the enormous increase in potential levels of radioactivity and to the variety of radionuclides associated with the fission process. It is, thus, primarily a saga of research done under the pressures of World War II. Only to indicate the settings for the work and some extensions into the postwar years, which are essentially part of a continuum, does it stray from the 1940 to 1947 era. As a result, much work done earlier on isotopes of elements such as iodine, phosphorus, sodium, potassium, etc., is omitted here. These were reviewed when we examined the accelerator-produced isotopes of the early and middle thirties in chapter 5. Some, for example iodine, will come back in our consideration of postwar research (chapter 8) and of nuclear medicine (chapter 20). Others, like xenon, krypton, etc., which are primarily an inhalation problem, are deferred to the special chapters on this subject (chapters 9 and 10). This is done despite the fact that some of these radioisotopes are indeed fission products. The new information on the properties of the two hundred or so new radioactive isomers developed in nuclear fission and its pertinence to biology and medicine and to protection standards are the main business of this chapter.

I. The Problem

Plans for protection of the personnel of the Plutonium Project against the enormous quantities of radiation and radioactive materials expected to be produced began even before it was certain that the chain-reacting pile would work. After December 1942, when the pile did work, the problem was fully upon them (and all of us).

The products of uranium fission include, besides the energy released as prompt radiation and recoil, over two hundred isotopes of thirty-four elements extending from zinc to europium. About sixty nuclides occur as primary reaction products. The rest develop through chains of radioactive decay of these primary products.

Many authors have already pointed out, but it is still pertinent to relate again, the scaling factor introduced by the facts of nuclear fission. In the nearly half-century since its discovery to the early 1940s, about one kilogram of radium (i.e., one kilocurie) had been extracted worldwide from its ores. Yet, as we saw dramatically in chapter 1, this amount had presented serious problems of toxicity to hundreds of individuals. The chain-reacting piles of the Plutonium Project would produce hundreds of megacuries, a scaling factor from radium of at least 10^6 , and this was only for the first phase of the effort.

Further, as Hamilton (1949) pointed out in one of the first publications on the work of the Plutonium Project, only one of these radionuclides, iodine, had been studied in enough detail prior to 1942 to allow a reasonable evaluation of permissible exposures. Radiostrontium had also been studied but not sufficiently to meet the needs of the Plutonium Project. All of the others required evaluation of metabolic properties and eventually of effects. Some could be gauged by analogy to other elements. But by and large the investigators were in virgin territory regarding the behavior and biomedical significance of about two hundred essentially new substances.^(a) Finally, decisions needed to be made in great haste to avoid possible catastrophic mistakes and gross overexposure of workers.

This was indeed a new dimension in internal emitter research. No more waiting for a former dial painter to show symptoms or x-ray changes in bone or the slow realization that the uranium miners were developing lung cancer. This chapter takes up the major biomedical researches done on the fission products during World War II. The following chapter will review the second major new dimension, that posed by the production of plutonium and the transplutonic elements. Later, we will review the postwar work on fission products and actinide elements.

That the efforts were successful, and the knowledge sufficient for the times is seen in the fact that "... throughout the entire wartime period of activity of the Plutonium Project, there was not a single known episode of manifest radiation injury to the thousands of persons who worked on this program" (Hamilton 1949, p. 863).^(b)

II. The Fission Products

Before examining the biomedical work, we need a short summary to define the area of interest. Excellent reviews of the fission process are, of course, abundantly available. One of the earliest, and still an excellent one, is the summary of previously classified literature found in Glasstone's *Sourcebook on Atomic Energy* (1950). A more recent and very useful exposition can be found in the now classic text by Lapp and Andrews (1972).

The energy of the fission process is divided among kinetic energy of the fragments, prompt radiation, and fission-product activity. Lapp and Andrews (1972, p. 358) give 11% as the proportion of the total initial fission energy going

(a) True, the radioelements were isomers of stable elements already known, but the radioactivity component had the effect of making them "new substances."

(b) In view of the long latent period of chronic radiation effects, this statement must be viewed as implying short-term, relatively acute effects. Also, it would not include any criticality accidents where the problem is the prompt radiation released.

into fission product activity. For present purposes, we will consider only this and not the other 89% except in passing.

The fissile nucleus does not necessarily split symmetrically. At the relatively lower energies associated with thermal neutrons, asymmetric fission is more probable than symmetric. Only at exciting energies on the order of 400 MeV is symmetrical fission the most probable reaction. Furthermore, each individual fission is a unique event. The composition of fresh fission products is thus the result of a large number of probabilistic events. Nevertheless a fairly characteristic composition is seen: the now-classic bimodal curve of fission yield versus mass number. An example is seen in figure 6.1.

Note that the curve is for fission at thermal neutron energies and that it differs somewhat depending on whether the fissile material is ^{233}U , ^{235}U , or ^{239}Pu . Remember, too, that this picture applies only to fresh fission products. The decay of the short-lived components and the expression of the fission product chains soon change the composition.

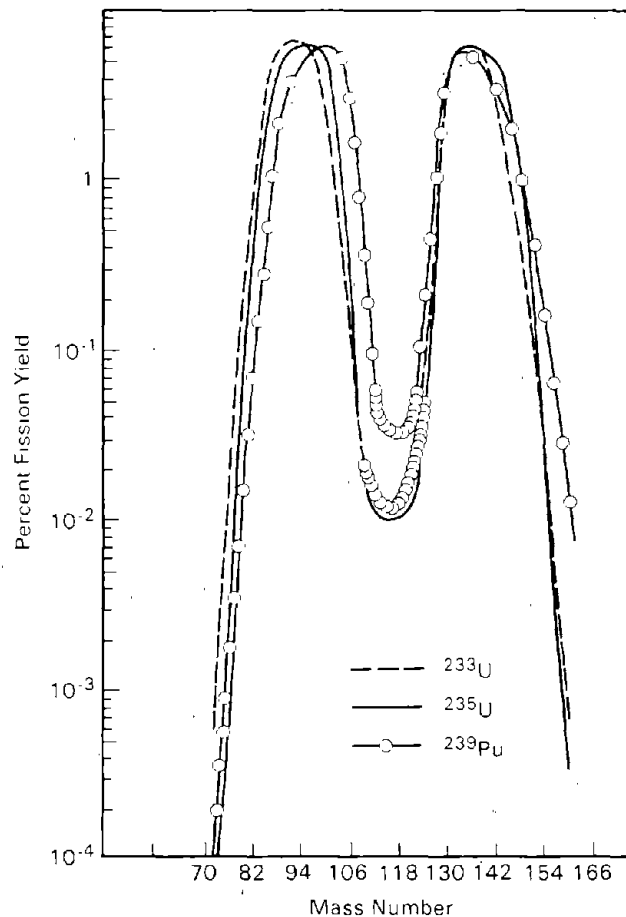


FIGURE 6.1. The classic bimodal curve for fission-product yield from ^{233}U , ^{235}U , and ^{239}Pu . (Redrawn from Lapp and Andrews 1972, p. 359. Reprinted with permission of Prentice-Hall, Inc., Englewood Cliffs, New Jersey, copyright 1972.)

As Glasstone eloquently pointed out, the mixed fission products soon after formation are mixtures of great complexity. Much research was necessary to devise methods for identification and isolation of individual products and chains. Fortunately for the biomedical scientist, some simplifications could be applied. First, the radiation dose from fresh fission products decreases as a power function of time, as might be expected from a mixture decaying exponentially with a wide variety of decay constants. The exponent varies with the starting material and energy of the exciting neutrons. The classic rule espoused by Way and Wigner (1948) is an exponent of -1.2 after the initial, very short-lived nuclides have decayed out.^(a)

Second, since a large number of the products have short half-lives and/or decay by chains, it is possible to identify a few nuclides of predominant importance to living organisms.

Third, the radiations are predominantly beta and gamma. Thus, to some extent the experience with x rays and radium gammas could be utilized for the gamma components. Entirely new research and theory were needed for the beta-particle effects. These had been studied with cyclotron-produced elements. Parker (1943) prepared an early informative summary.

The challenge to biomedical research on the fission products was to identify those elements of significant fission yield, of sufficient half-life to be significant yet not so long as to deliver only a minuscule dose over times of interest to worker protection, and then zero in on characterization of their metabolic behavior and their acute and long-term effects. Obviously, such a simplification was essential. It was successful as we shall see. There was also need to characterize the biomedical problems of mixed fission products. This was emphasized in research on the characterization of the quality and quantities of radiation emitted under different conditions of production, storage, and eventual handling of fission products as nuclear waste.

III. Tracer Studies at Berkeley

A. The Modus Operandi

The cyclotron at Berkeley that produced many of the radioisotopes discussed in chapter 5 was a 37-in. machine housed in an old wooden building called "The Radiation Laboratory" (a far cry from the radiation laboratory of later years). Near the end of the decade of the 1930s, the University of California at Berkeley acquired two buildings that have played host to much important biomedical research. The first was the Donner Laboratory. The second was the Crocker Laboratory, sponsored by a San Francisco banker whose family fortunes had come from the gold rush and the Southern Pacific railroad. The latter was opened in 1939, and almost immediately a 60-in. cyclotron was installed in it. Combined with the older 37-in. machine, which remained in the Radiation Laboratory, this machine enabled much progress toward providing fission products for biomedical research in the early years of World War II, even before the nuclear fission reaction had been proven feasible.

Hence, as war work began to look inevitable, the Berkeley laboratories were not only fully prepared, they were already under way to a degree. The Donner

(a) The more complete formulation is $\frac{dE}{dt} = (3.9t^{-1.2} + 11.7t^{-1.4}) \times 10^{-6} \text{ MeV sec}^{-1}$ (Lapp and Andrews, 1972, p. 366).

Laboratory was partly diverted from things biomedical and became headquarters for Ernest Lawrence's wartime team, a host of visitors, and the Calutron Project administration. A young physician, Joseph G. Hamilton, whom we met in chapter 5, and who had plans for a major effort with ^{32}P for the treatment of leukemia, was chosen to direct the Crocker Laboratory. Interestingly enough he even had ideas for possible therapy of bone tumors with a new radioisotope of strontium which was found to localize in bone (Pecher 1941; Pecher and Pecher 1941).

A systematic study of the metabolism of the fission products of uranium was begun on October 15, 1942. Note that this preceded by about two months the success of the chain-reacting "pile" in Chicago. The fission products were derived from the bombardment of uranium targets by deuterons in the 60-in. cyclotron, not from nuclear reactions in a pile (reactor). They continued to be so produced throughout the work, long after pile-produced fission products could be made available. The reasons for this were largely technical. The problems of preparing carrier-free isotopes from the cyclotron targets had been or were being worked out satisfactorily. It was a long time before comparable separations could be made from the complex mess of reactor fission products. Also, the radiation levels from the products of the cyclotron were much easier to cope with than reactor fission products. Thus, it seemed better to proceed as rapidly as possible with a well-established technique.

But the quantities of fission products produced in the cyclotron were quite limited. Thus, all of the Berkeley experiments were strictly at the tracer level. No studies of effects could be done there. These were performed in other parts of the Plutonium Project.

Hamilton was joined in the endeavor by several whose names will not be forgotten. One was Kenneth Scott, a recent graduate student who had already been involved with possible therapeutic uses of isotopes. Others included Harold Copp, Dorothy Axelrod, Josephine Crowley, Henry Lanz, Lester Van Middlesworth, and, as a technical assistant, Patricia Wallace (now Patricia Durbin), who provides invaluable continuity to the entire effort. (More in chapter 8.) Advice was made available by senior scientists such as I. L. Chaikoff and D. M. Greenberg and, of course, it all grew under the watchful eyes of Robert Stone and Ernest Lawrence. Early in the project, Hamilton persuaded two soil scientists from the Agriculture School who were not involved in war work to join him as chemists. These were Roy Overstreet and Louis Jacobson, who did the majority of the radiochemical preparations of the carrier-free fission products from the irradiated targets.^(a,b)

- (a) While the personnel involved in the Berkeley work are identified in the monthly and other progress reports, as well as in the later publications, referenced in the bibliography to this chapter, much personal and anecdotal information was obtained from Dr. Patricia Durbin who began work at the Crocker Laboratory as a "Diener" in July 1946 and who has been there ever since. I am greatly indebted to her for a personal interview in October 1979 and for a transcript of a paper she gave at a history session of the combined Health Physics and Radiation Research Society meetings in San Francisco in July 1974. The latter was not published, but the organizer and chairman of the program, Dr. Ronald Kathren, provided me with a transcript of the tape.
- (b) While all of the war enterprises were strictly group efforts, each had its key personnel. A fascinating review of the chemistry group at the Metallurgical Laboratory has been provided by Seaborg (1977-1980). We cannot provide the same detail, but Appendix B attempts to provide a much-compressed "Who's Who."

Reports of the California work began to appear almost immediately in the classified monthly reports of the Plutonium Project. A few selected ones are given in the reference section under Metallurgical Laboratory (1942; 1943a,b,c; 1945a,b; also Hamilton 1943b, 1944).^(a)

By 1945, summary-type reports began to appear (e.g., Hamilton 1945). Others were prepared for what was known as the Project Handbook.^(b) Many were included in the National Nuclear Energy Series (NNEs) volumes, including some that were never published. (See "NNEs Hiatus," Appendix C, where the paper titles are listed and the abstracts given.)

A very complete summary document was prepared by the California groups before declassification permitted open literature publication. It was later available as a Manhattan District Declassified (MDDC) report (Scott et al. 1947). With 209 pages, this report gives more detail on the preparation of the materials than any of the published works. It has separate chapters for strontium, barium, yttrium, cerium, praseodymium, zirconium, ruthenium, tellurium, iodine, xenon, cesium, and "Fission Product Mixture." Fortunately, except for the important information on techniques and that on the fission product mixture, all of the information also reached the open literature (Hamilton 1947, 1948).

B. The Results

A fairly standard format was used: three rats per group and usually four elapsed time periods per isotope and per dose. Thus, twelve rats were involved for each progression, three for each point. This has been viewed as marginally small by many subsequent investigators. Yet, the information gained in these almost pilot-type experiments has stood up exceedingly well. And it should be remembered that amounts of the isotopes were quite limited. Indeed, there was not enough for three rats per point in some instances.

In addition to the two published reviews by Hamilton already cited, a rather similar one was published in the *New England Journal of Medicine* (1949), and declassified papers on specific elements were scattered through both the Atomic Energy Commission (AEC) and the regular published literature. A most useful compendium on strontium and calcium is the one by Wasserman and Comar (1961), which gives an insight into both the Project literature and subsequent published papers.

Tracer studies involved parenteral injection, oral ingestion, and intratracheal instillation. Since the results of the latter work were only qualitative, it will not be discussed here. In addition to radiochemical measurements, there was an extensive program of autoradiography, which was employed to characterize distributions within tissue. The quantities administered were usually in the range of 0.58 to 5.0 μCi , thus assuring no modification of transfer kinetics and localization by radiation damage. Feces and urine were separated in special metabolism cages developed in the Department of Physiology.

(a) Few complete sets of these monthly reports now exist. The most useful set is in the hands of Dr. Hymer Friedell, professor of radiology emeritus at Case-Western Reserve Medical Center. I am much indebted to Dr. Friedell for the opportunity to go through his files and make copies of the most pertinent documents.

(b) This became the basis in part of the postwar monographs prepared in each laboratory and known as the National Nuclear Energy Series. We will cite many of these as we progress.

Sometime in 1943, a summary table (table 6.1) was prepared (Durbin 1976). Information on fourteen fission products could be given, including parameters such as oral absorption, accumulation in principal organs of retention, and rate of elimination therefrom. Consider that this was from a project begun in mid-October 1942! Under today's conditions, the paperwork for the supporting funds would have barely been completed in that period of time.

TABLE 6.1. Summary of Early Fission Product Studies

Radio-element	Half-life	Fission Yield (%)	% Oral Absorption	% Accumulation in Principal Organ of Retention	Rate of Elimination from Principal Organs of Retention	
Sr ⁸⁹	53 d	4.6	5-60	70% bone	bone	>200 d
Sr ⁹⁰	25 yr					
Ba ¹⁴⁰	12.8 d	6.1	5-60	60% bone	bone	>50 d
I ¹³¹	8.0 d	2.8	100	20% thyroid	thyroid	>30 d
Cs ¹³⁵	33 yr		100	45% muscle	muscle	15 d
Y ⁹¹	57 d	5.9	<0.05	65% bone	bone	>500 d
La ¹⁴⁰	40 hr	6.1	<0.05	70% liver	liver	10 d
				30% bone	bone	>25 d
Ce ¹⁴¹	28 d	5.7	<0.05	50% liver	liver	10 d
Ce ¹⁴⁴	275 d	5.3	<0.05	25% bone	bone	>100 d
Pr ¹⁴³	13.8 d	5.4	<0.5	35% liver	liver	10 d
				50% bone	bone	>100 d
61 ¹⁴⁷	3.7 yr	2.6	<0.05	55% liver	liver	10 d
				35% bone	bone	>100 d
Zr ⁹⁶	65 d	6.4	<0.05	35% bone	bone	>100 d
Nb ⁹⁵	35.15 d	6.4	<0.5	30% bone	bone	30 d
				25% blood	blood	1 d
				3.5% kidney	kidney	20 d
Ru ¹⁰³	42 d	3.7				
Ru ¹⁰⁶	1 yr	0.5	<0.05			
Te ¹²⁷	90 d	0.033	25	15% blood	blood	15 d
Te ¹²⁹	32 d	0.19	25	6% kidney	kidney	15 d
Xe ¹³³	5.3 d	4.5				

Source: Modified and reset from Durbin 1976.

By February of 1944, the first phase of the fission product work was completed, and the first samples of plutonium arrived for metabolic study. This captured the lion's share of interest at Berkeley from then on. A table similar to table 6.1, but listing also the properties of plutonium and related elements, is given in the Berkeley group's first major open literature publication (Hamilton 1947), from which the following salient points concerning fission products can be summarized:

1. Localization in bone is quite common after parenteral administration.
2. Only five of the studied fission products are absorbed significantly from the digestive tract. These are strontium, barium, tellurium, cesium, and iodine.
3. The pattern of distribution following oral absorption is indistinguishable from that after parenteral administration.
4. As was already known, iodine deposits selectively in and is retained fairly avidly by the thyroid tissue.

5. Some of the nuclides deposit initially to a considerable degree in liver but leave this organ quite rapidly while being retained by bone. These are lanthanum, praseodymium, cerium, and what was then known as element 61 (now promethium). This deposition did not appear to be in reticuloendothelial system (RES) elements since spleen and bone marrow did not show similar accumulations.
6. Other soft tissues retained relatively small amounts, although spleen and kidney might reach from 0.1 to 0.25 of the bone content after two months or more.
7. Xenon acts entirely independently as would be expected from a relatively unreactive gas. It is quickly absorbed through the lungs and quickly eliminated.
8. Loss from bone is usually quite slow, as illustrated in figure 6.2, taken from Hamilton (1947). (Contrast the picture shown in figure 6.2 with that seen for the deposition and elimination from liver as shown in figure 6.3, also taken from Hamilton 1947.)

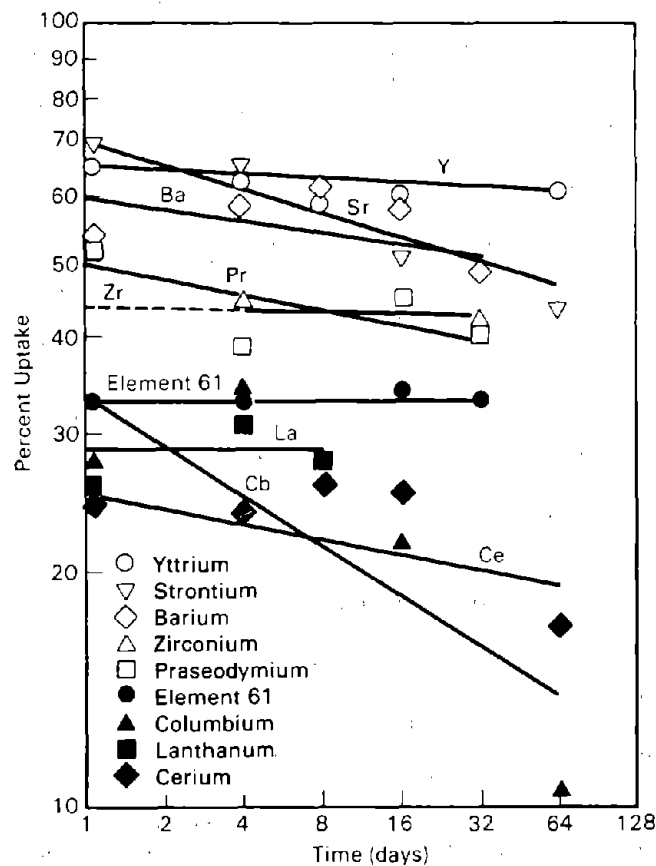


FIGURE 6.2. Early depiction of bone uptake and retention of several fission products as indicated. (Redrawn from Hamilton 1947, p. 329. Reprinted with permission of Radiological Society of North America, Oak Brook, Illinois, copyright 1947.)

These results did much to simplify the problems of understanding these new radionuclides; particularly in the context of worker protection. The alkaline earths and rare earths deposited in bone, with or without temporary residence in other tissues like liver. The experience with radium could be applied to these, *pro tem* at least, with appropriate corrections for the different metabolisms.

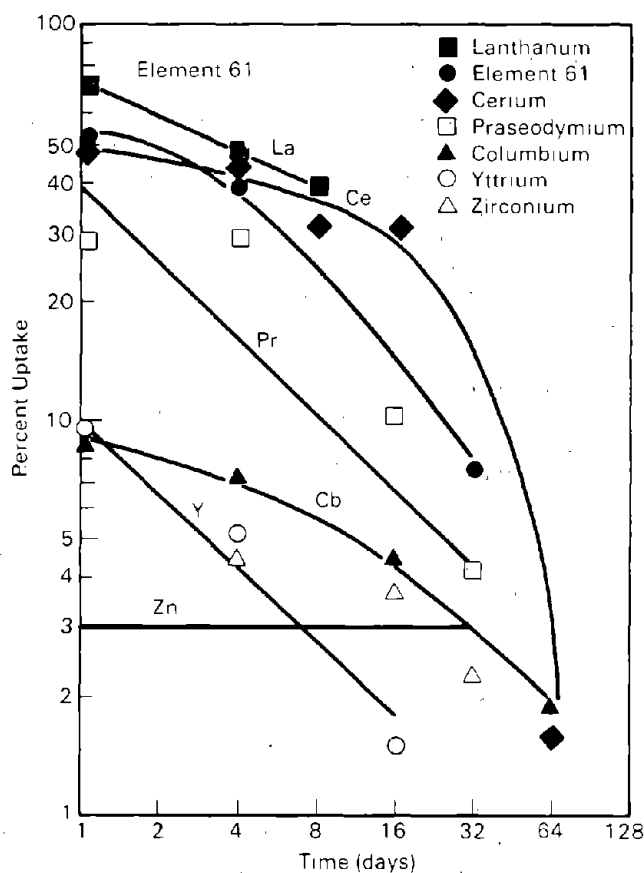


FIGURE 6.3. Illustration of the relatively rapid elimination of several fission products from liver. (Redrawn from Hamilton 1947, p. 331. Reprinted with permission of Radiological Society of North America, Oak Brook, Illinois, copyright 1947.)

The remaining five fission products from the list of biomedically important ones, ruthenium, tellurium, cesium, xenon, and iodine did not localize to any degree in skeleton. But, except for the special case of iodine, they showed no marked concentration in any other tissue, and they were excreted much more

rapidly than the bone seekers. On this basis, it could be concluded that these elements did not pose as great a hazard as the alkaline and rare earths.^(a)

The work with purified, uranium-free but unseparated fission products appeared largely in Project reports, e.g., Scott et al. (1947). The mixture used was "cooled" eighty-seven days before injection. While there were some puzzling inconsistencies, on the whole, the mixture behaved like a summation of its components, largely strontium and barium.

The autoradiographic work, seen to largely it seems by Dorothy Axelrod, brought some surprises. These are pertinent to the current chapter and even more pertinent to our consideration of the actinides and transuranic elements. Figure 6.4 is a now classic picture showing a photomicrograph (upper) and an autoradiograph (lower) of the femur of a rat one week after receiving 5 μ Ci of radioactive strontium (presumably ^{89}Sr). The autoradiograph shows the strontium deposited relatively evenly through the mineral structure. This was much like radium and calcium, and no surprise. But practically none of the other bone-seeking fission products showed such a distribution. Instead, they, like plutonium (see chapter 7), were deposited on endosteum, periosteum, and in the region of trabecular bone. Yttrium, zirconium, and cerium behaved in this manner. An illustration taken from Hamilton's review (1947) is seen in figure 6.5. The adult rat received 10 μ Ci of zirconium and was sacrificed twenty-one days later.

Clearly, the microdistribution of the radiation dose from such a deposition would be quite different from that characteristic of strontium and radium. It was now clear that there were at least two kinds of bone-seeking elements. The ramifications of these findings, seen first in the Berkeley work, have occupied the attention of those interested in bone-seeking elements and the physiology and biochemistry of bone ever since.

This summarizes the major findings from the broad exploratory work at Berkeley. With a group so large and diversified, obviously there was some

(a) An indication of the general tendency to use the results for gauging of hazard can be found in the following excerpt from a letter to C. M. Cooper from J. G. Hamilton, dated July 27, 1943, on Metallurgical Laboratory stationery:

I should like to point out in the first place that under these circumstances radio-ruthenium, on the basis of its abundance, is far more of a potential hazard than either the 8 day Iodine or the 5 day Xenon, since these two radioelements have relatively short half-lives and their abundance at the time of chemical extraction would be many times less than that of the ruthenium. In addition, the beta-rays from the 30 second rhodium daughter of the 200 day radio-ruthenium are extremely energetic. It was my understanding that present plans at W contemplate the use of either tetra-valent cerium or bismuthate as the oxidizing agent for the product. As you recall under these conditions ruthenium is converted to the volatile tetroxide, Dr. Coryell told me today that they found under small scale test conditions as much as 15% of the ruthenium present in the solution was volatilized during the oxidation. You may recall from the discussion at the Laboratory Council Meeting of July 12th that it was stated that ruthenium when introduced into the lungs was retained to a high degree for periods of time ranging up to 16 days. In this particular instance the ruthenium was introduced in the tetra-valent state. However, it is probable that any ruthenium tetroxide which might be inhaled would be very promptly reduced by the tissue fluids within the lungs. The experimental work in Berkeley indicates that some of the fixed ruthenium in the lungs will be slowly released and eliminated. . . .

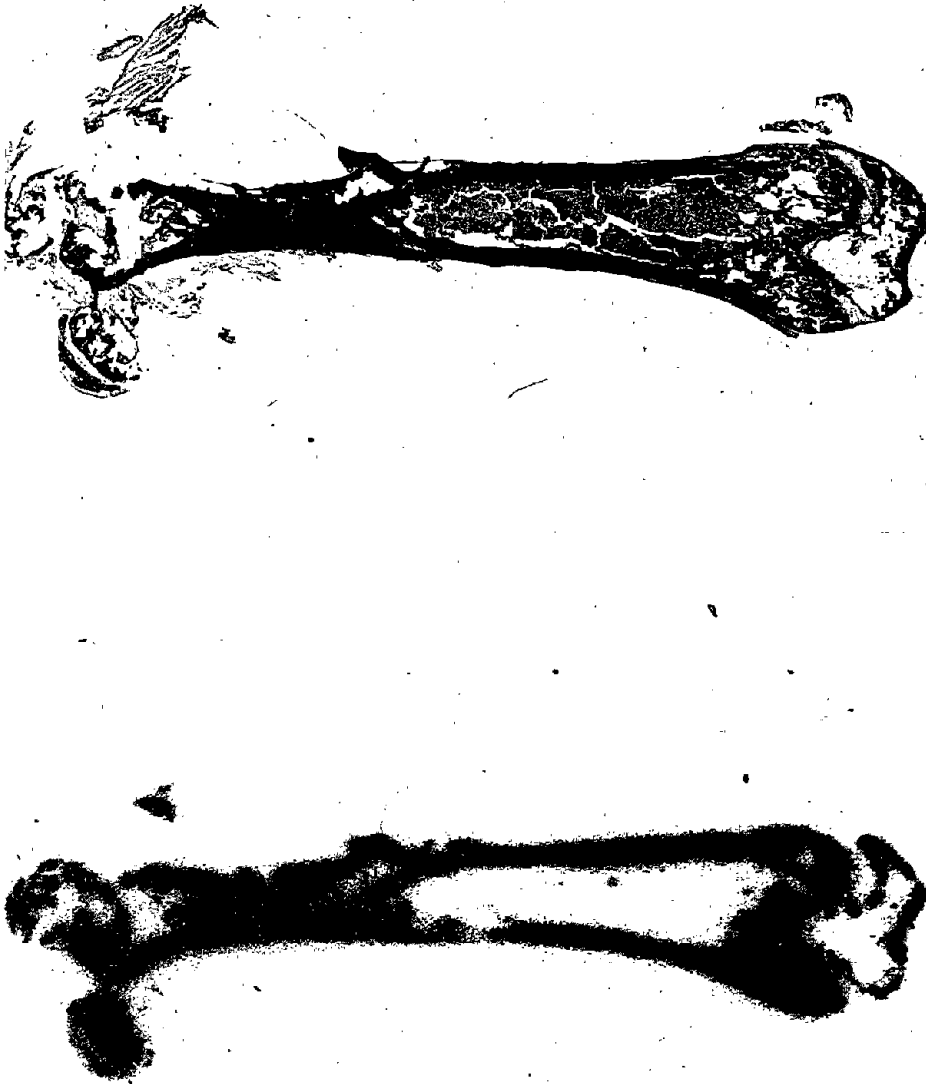


FIGURE 6.4. Early photomicrograph (top) and autoradiograph (bottom) showing distribution of radioactive strontium in rat femur one week after intraperitoneal injection. Note the distribution to the sites of bone mineral and deposition in calcifying trabeculae beneath the epiphyseal plate. The similarity to calcium is notable. (From Hamilton 1947, p. 333. Reprinted with permission of Radiological Society of North America, Oak Brook, Illinois, copyright 1947.)



FIGURE 6.5. Early photomicrograph (top) and autoradiograph (bottom) of rat femur 21 days after injection of radiozirconium. Note the lack of deposition in mineral matrix. Zirconium is just one of several fission products that appear to be “surface” rather than “volume” seekers (see text). (From Hamilton 1947, p. 337, utilizing in part data from unpublished wartime studies. Reprinted with permission of Radiological Society of North America, Oak Brook, Illinois, copyright 1947.)

opportunity for peripheral investigations. When it was clear that the elements of most concern among the fission products were bone seekers, Harold Copp and his group investigated possible therapeutic removal. This was much like the work described for radium in chapter 1, and was about equally unsuccessful. Age was studied as a variable, and the expected greater uptake by the young was shown. Mechanisms were mused about even though time did not allow much active research to check out ideas. The facts of bone remodeling began to emerge (Jones and Copp 1948). Effects of diet and disorders such as rickets were looked at (Jones and Copp 1951).

A comparison of radiostrontium uptake by adult, young, and young rachitic rats taken from the work of Copp and colleagues and presented by Durbin (1976) is shown in figure 6.6.

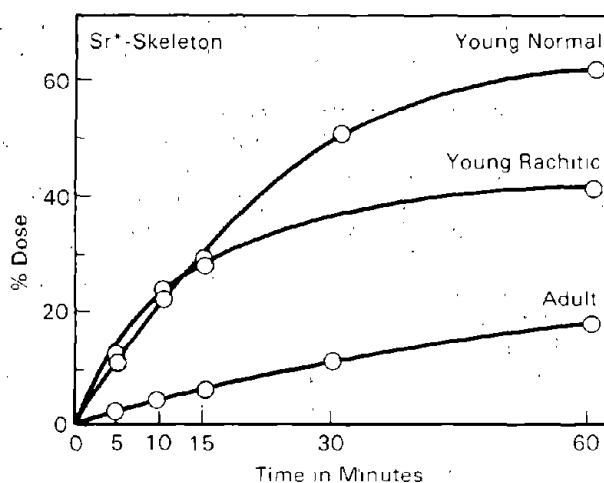


FIGURE 6.6. Comparison of strontium uptake by young normal, young rachitic, and adult rat skeleton. (Redrawn from Durbin 1976.)

Toward the end of the period, the Berkeley group added some bona fide inhalation experiments with characterized aerosols of fission products. These substituted for the earlier unsatisfactory intratracheal instillation work. Discussion will be reserved for the chapter on inhalation toxicology (chapter 9).

Finally, it is pleasing to see that Jacobson and Overstreet, who had been recruited into being the radiochemists, got a chance to use some of the radio-nuclides at hand in experiments related to agriculture—their home base. They published a study of the mechanism of ion absorption by plant roots using isotopes of rubidium, strontium, and iodine (Jacobson and Overstreet 1947) and an in-house report on uptake of yttrium, cerium, strontium, tellurium, zirconium + columbium, as well as plutonium by barley and dwarf pea plants (Jacobson and Overstreet 1945).

There were many others, but these should give the flavor of the “side-show” researches accompanying the main study, along with the fact that the main study turned to the inhalation route, the most likely mode of worker exposure, when adequate quantities of material and techniques were available.

C. Postlude at Berkeley

The end of World War II did not end fission product research at Berkeley or anywhere else. Indeed, after a short interlude, work was resumed with new vigor and in new dimension as we shall see in chapter 8 and others. Yet, an era ended for the Crocker Laboratory during the immediate postwar years.

First, there were personnel changes. Ken Scott went across the Bay to the medical campus in San Francisco to run its radioisotope laboratory. Jacobson and Overstreet went back to the School of Agriculture. Harold Copp went to British Columbia. The Donner Laboratory became again a medical research institution, and John Lawrence returned to his brother's side and managed space and finances for training, both formal and apprentice-type, of scores of "students," many of them quite senior coming to learn about the new field of atomic energy and radioisotopes.^(a) Formal courses were started, including one by Joe Hamilton. Pat Durbin obtained a Ph.D. in chemistry and became much more than the diener and animal tender she says she was during the war (Durbin 1976, 1979).

Nevertheless, and despite these other activities, Hamilton and his staff continued tracer studies with fission products going on to the less abundantly produced elements. Durbin relates that this process was known affectionately among the staff as "chewing our way through the periodic table" (Durbin 1976), remarking that next to the 60-in. cyclotron the periodic table held the greatest fascination for Joe Hamilton. By 1959 to 1960, most of the elements from fission and many others of interest had been studied. Attention turned to problems that there had not been time to attack during the war years. This resulted in (1) a University of California Radiation Laboratory report on the localization of ^{144}Ce in fetal rats, (2) a study on the distribution in the rat of radioisotopes of some heavy metals, and (3) a study of the lanthanides. These are detailed in chapter 8.

Joe Hamilton died of leukemia in 1957. In 1960, the 60-in. cyclotron was dismantled, and later the laboratory became a parking lot. The cyclotron magnet is at work in a reincarnation of the Crocker Laboratory built on the campus of the University of California at Davis (Durbin 1976; Seaborg 1980). The 37-in. cyclotron from the old "Radiation Laboratory" now resides in the Lawrence Hall of Science on the Berkeley campus. Its large magnet was used during the war years in the Calutron project.

A photograph of the Crocker Laboratory at Berkeley is shown in figure 6.7.

IV. Fission Product Research at Chicago

A. The Modus Operandi

Work on the fission products in the Chicago section of the Metallurgical Laboratory seems not to have begun so early nor to have been so neatly packaged as the work at Berkeley. The early monthly reports speak first to setting up apparatus for study of radioactive xenon (Metallurgical Laboratory Monthly Reports, September 1942, February 1943, et seq.), also for xenon and argon together. Very soon, they address subjects such as "Hazard from Inhaled ^{131}I "

(a) Even during the war nearly everyone had at least a few months at Berkeley; but then it was all classified and in very specific one-to-one relationships, which waxed and waned as quietly as possible.

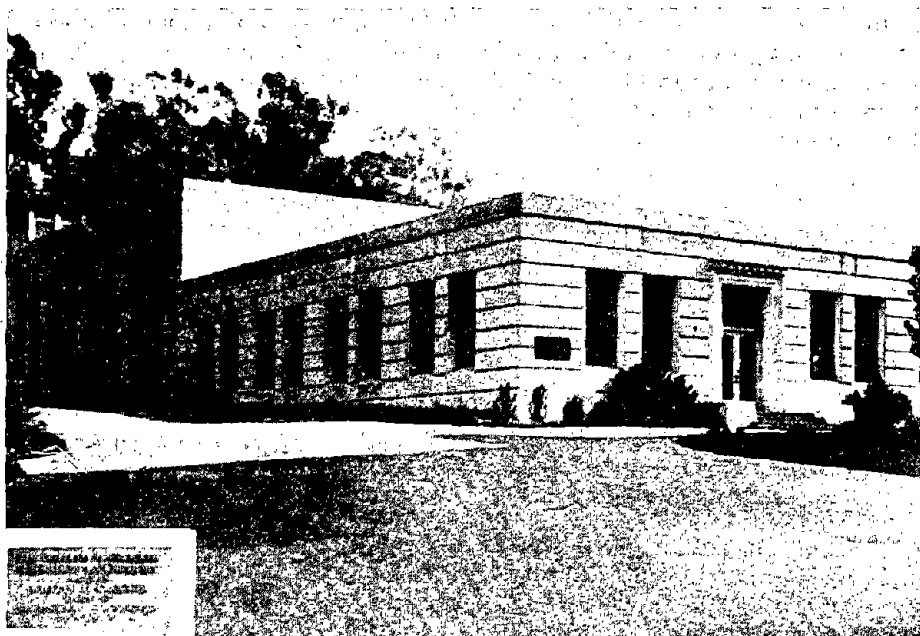


FIGURE 6.7. Photograph of the Crocker Laboratory on the University of California Berkeley campus, home of the 60-in. cyclotron and much of the early work on fission products and actinides. Building has been demolished since this photograph was taken. (Courtesy of Dr. P. W. Durbin.)

and "Hazards from Fission Products." Results are only sketchily given in the monthly reports. In the early months, more attention was paid to other plans for the Chicago project.^(a) But by April 1944, a substantial section was devoted to "radioactive materials, mammals." This section includes xenon, ruthenium, iodine, ^{89}Sr , ^{140}Ba - ^{140}La , ^{32}P , and fission product mixture in small rodents, along with descriptions of the distribution and effects of fission mixture in goldfish. But biological results do not begin to appear in earnest until the monthly reports of early 1945. From then on, there was a mounting crescendo of inhalation, ingestion, and comparative toxicity experiments from the Chicago group.

The reasons for this different tempo and approach at Chicago compared to Berkeley appear to be at least twofold. First, the orientation was more toward effects, i.e., toxicology, in addition to the metabolic behavior of the elements. Second, the much larger quantities of material thus needed required waiting for a supply of fission products from the reactor at the Clinton Laboratories in Oak Ridge, which started operation in the latter part of 1944.

We have already addressed the early problems of establishing techniques for fission product separation and purification, but they need some elaboration. A typical example of what had to be gone through initially to get fission products,

(a) The general problems of uranium toxicity, personnel protection, neutrons, and external radiation filled these early reports along with projections for the Berkeley work.

in this case radiobarium and radiostrontium, ready for biological use is seen in the following letter, reproduced in part, from Waldo Cohn to R. D. Finkle dated December 1943 (Cohn 1943). Dr. Finkle was preparing to manage a block of the fission product work at Chicago, and Dr. Cohn was at the "pile" at the Clinton Laboratories.

Dear Ray:

... At this time we had all the Ba and Sr of the PbSO_4 precipitates, (except the 95 mC) in two small tubes, one being the BaCl_2 precipitate, the other the supernatant which should contain the Sr. The lead had gone over to the Sr in the course of HCl-ether washings of the Ba precipitate, we reasoned (and no PbS came down on testing with H_2S).

The Sr fraction was cleared of Ba by adding another 0.5 mg Ba, evaporating, dissolving in 0.5 cc and adding 5.5 cc of HCl-ether mixture (4-1/2:1). The precipitate turned out to have 6-1/2 times the activity of the first Ba precipitate. Since the chemical Ba was the same we decided to combine both Ba precipitates. We now had an Sr solution free of active Ba, containing Pb, and two 0.5 mg Ba precipitates. Okay so far?

At this point I had better warn you that our assays with survey meter of Hume's counter have been found to be in error due to at least two factors: one, contamination of glassware due to absorption—hot, strong acid seems to be the only way to get all adsorbed activity out; two, contamination of glassware due to the deposition by recoil in the structure of the glass itself of daughter La from Ba decomposition. This can't be removed. Hence some of our tubes and flasks had high counts to start with (unbeknownst to us) and we had no guarantee that all the activity in a container would come out easily or dissolve for reprecipitation, etc. Also, we were depending on γ activity for such scouting. Lastly, every container or pipette used adsorbed some of the activity. This we are recovering along with the losses to be mentioned in a moment.

... I can't impress on you too strongly the need for devising ways and means to get around adsorption and contamination. We are designing leucite containers and syringes for shipping and injecting; we will try to get such built quickly. We may have to use 1 or 1/2 mg of carrier, since the slugs are too pure, until we can lick the adsorption problem here.

Hand and apparatus contamination have plagued us throughout. The whole lab must be thoroughly cleaned up to be safe. Nor would a "hot lab" have helped us to do anything on prevention of hand and body overexposure. Two things will: more manpower per operation, and a great deal of care and forethought in devising and planning experiments and equipment to do the job safely. We have been the first to do such work on the Curie-level, and we have learned a lot about how not to do it. We think we know now how to proceed, but we must build the equipment and work more slowly at first. So don't rush us; we are piloting a rather dangerous and tricky business. If you can spare manpower, for a week or ten days, we can move faster. There are only three of us to do the job, and this is the place to do it.

If Ed gets over 5 mC Ru we will send it up with the Sr and Ba now going through. Then, after scrubbing the lab, we will try for 200 mC of mixed F.P.s. And it is no hand job—not with what we know now.

(Cohn 1943, pp. 1, 3)

B. Results

Full-length papers from the Chicago work were issued first as classified in-house reports. Many of these were later prepared for the three volumes of the NNEs that did not get published (Appendix C). Others were issued only as declassified in-house documents and were not slated for publication. Many reached the

published literature in the immediate postwar period or were presented in part in various summaries and symposia.

1. Earlier Work

A general review of this earlier work gleaned primarily from in-house reports is given below:

a. A report by Tompkins, Broido, and Teresi (1946) gives a further insight into the development of radiochemical procedures used in much of the Chicago work on fission products. A quotation from the first page follows:

... This program involves the study of the biological effects of radioactive isotopes, including the products of uranium fission, which must be prepared in a radioactively pure form without added carrier and with very little extraneous solids.

At the time the laboratory was established, none of the fission products was available in pure form, so the emphasis was principally on the separation and purification products without added carrier. As this work was taken over by the Clinton Laboratories and stock solutions of purified radioactive isotopes became available, the operations in the laboratory were reduced to the withdrawal of aliquots of these stock solutions and the preparation of these aliquots for use in the Section. Since preparations were diversified, it was not feasible to develop a special apparatus for each preparation. The techniques and equipment have, therefore, been developed to approximate standard laboratory practice as closely as possible. The principal requirement has been for the handling of pure beta emitters at levels under 100 mc since most of the experimental work has been concentrated on the use of this type of material.

The paper describes the many special tools they devised for handling the beta and beta-gamma emitters, with special emphasis on avoiding what they considered the worst hazard, reaching over a shield and working from above the "hot" sources.^(a)

b. The barium-lanthanum couplet was investigated quite early. A brief description of the methods employed is given in a report by R. D. Finkle, Snyder, and Tompkins (1946), and the metabolism and acute radiotoxicity by Snyder et al. (1946). An important objective of the experiment was to compare the metabolism of toxic levels with the tracer levels used in the work at Berkeley. They were strictly comparable in general except that large (i.e., lethal) doses were retained more completely in the skeleton of the rat than lower doses. Effects of the barium-lanthanum couplet on weight and food intake (Snyder, Sacher, and Teresi 1946) showed definite growth retardation at about half the midlethal dose for each species. The midlethal dose in one month was about 3 to 5 $\mu\text{Ci/g}$ (R. D. Finkle, Snyder, and Kisieleski 1947). Finally, Jacobson (1946) reported that the hematological effects were of the threshold type and indicated damage to

(a) Radiochemical purity of these sources has not been fully established. In the atmosphere of urgency, the Chicago investigators had to be satisfied with what they got, although checks were made that would have detected any gross errors or mislabeling. The purity improved rapidly with time as techniques were perfected. But we must assume that some of the earlier preparations had up to 10% contamination, perhaps more, especially with closely related isotopes such as ^{90}Sr in ^{89}Sr , ^{239}Pu in ^{238}Pu , ^{241}Am in ^{239}Pu , etc. (Kisieleski 1980; Norris 1978). The investigators closest to the work did not view the problem as serious, and it was relatively transient. But it does appear that the composition of injection solutions was largely taken on faith from the label and shipping information. Even at the time, tracing to specific batches at Oak Ridge was difficult, and it is, of course, impossible now (Kisieleski 1980).

bone and marrow because of deposition of the barium in bone and damage to spleen, lymphatic, and epithelial tissues primarily from the lanthanum deposited in soft tissues.

c. Among the early reports concerning metabolism and acute effects of strontium is a series by David Anthony and colleagues (Anthony, Lathrop, and R. D. Finkle CH-3844, MDDC-1540, no date; Anthony, Lathrop, and R. D. Finkle CH-3846, MDDC-1363, 1947; Anthony, Lathrop, and Snyder CH-3845, MDDC-1364, 1946; Simmons and Jacobson, CH-3797, MDDC-1387, 1946). The rapid loss from the body in the first three days noted in the Berkeley work was reiterated and expanded to include mouse and rabbit. After ten to fifteen days, virtually no more strontium was excreted. There were species differences in total excretion, however, with the most occurring in the rabbit and the least in the rat. The acute lethal dose in thirty days (LD_{50}) was between 7 and 8 $\mu\text{Ci/g}$ of ^{89}Sr - ^{90}Sr when received by the intraperitoneal route in mice, somewhat less, about 5 $\mu\text{Ci/g}$, in rats and rabbits. Concentration in bone after the first three days was more than one hundred times that in soft tissue. Blood changes were of the threshold type, with heterophils being the first to show changes.

d. An interesting correlative experiment was done with ^{32}P . This is, of course, not a fission product and was available before the war in sufficient quantity to support metabolism studies in humans and a beginning of therapeutic use. On premises akin to those for the use of radium as a bench mark, Anthony and Snyder (1947) embarked on a toxicologic study of ^{32}P for correlation with and as something of a base line for the fission product studies. A rather extensive program was planned, but only the so-called pilot studies could be completed because of the exigencies of other war work.

Nevertheless, the results were considered important for the possible extrapolation to man of work with the less-known newer elements, and they facilitated planning of later work.

To quote from the abstract of MDDC-881 (Anthony and Snyder 1947):

1. Data were obtained on the toxicity of a well-known radioactive element in the same strains of animals and under the same experimental conditions as data obtained with less familiar radioactive elements. Determinations of the relative radiotoxicity of different isotopes could therefore be made without reference to work done under different conditions.
2. Since the effects of radioactive phosphorus on man had been studied, comparison of the effects with those on laboratory animals provided a basis for extrapolation with other radioactive elements.
3. The experiments with radioactive phosphorus greatly facilitated planning and interpretation of later experiments on the toxicity of other heretofore rare radioactive elements.

The animals (ABC mice) received doses from 8.4 to 0.55 $\mu\text{Ci/g}$ by intraperitoneal injection. There were two series, one for metabolism and toxicity and one for serial sacrifice and study of pathology.

Retention in tissues is shown in figure 6.8, reproduced from figure 3 of the subject document.

Loss is quite rapid except from femur and brain and seems to be consistent with a power function of time, which appears with impressive regularity in most of the Chicago metabolism work on bone-seeking elements. There was no significant effect of dose on the pharmacokinetics. The LD_{50} is in the vicinity of

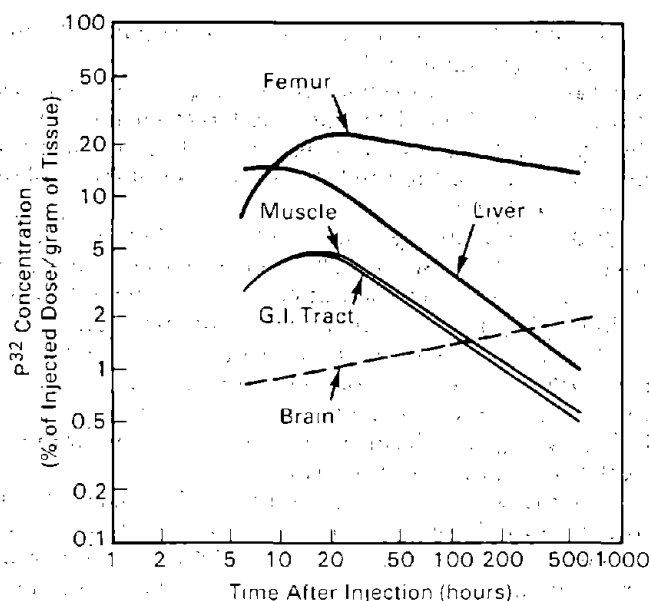


FIGURE 6.8. Concentration of ^{32}P in femur, liver, muscles, gastrointestinal tract, and brain. (Redrawn from Anthony and Snyder 1947.)

4 $\mu\text{Ci/g}$ body weight, but the experiment was too small to attach great significance to the figure. For what it is worth, it appears similar to that of the fission products.

There were no grossly visible lesions in the mice that died acutely. Some survivors developed tumors, but these are not discussed.

e. Cerium was in some respects a more complex problem than strontium. A considerable portion of an initial dose of cerium deposits in liver, while the rest goes to bone. Its distribution represents the rare-earth and rare-earth-like group of radioelements, which includes yttrium. Cerium-144 has a fairly long half-life (275 to 300 days) with a shorter-lived (17 to 18 min) daughter, ^{144}Pr , which is highly energetic (~ 3 MeV). The initial deposition in liver gradually leaves and goes to bone or is excreted. Unlike strontium, excretion of these is relatively slow.

The early changes involved liver more than bone with sometimes very few of the common lesions noted in radiation toxicology. The LD_{50} for 30 days in the rat was about 3 $\mu\text{Ci/g}$ and for 120 days somewhat lower.

2. Fission Products as Carcinogenic Agents

As soon as the work on acute toxicity was well established, the Chicago workers began to think about potential carcinogenicity of the new elements produced in fission. Because of the experience with radium, attention focused on the bone seekers. "The Manhattan District was determined not to encounter a delayed surprise such as that which greeted the radium painting industry. . . ." (MDDC-145, p. 1). But the interest extended as well to soft-tissue cancers.

A rather considerable effort was mounted quite early in the Met Lab's work. A major portion of the experiments concerned ^{89}Sr and plutonium, but there

were pilot experiments with radium, cerium-praseodymium, ^{91}Y , and the effect of age on bone tumor development.

The first moderately complete report of this large experiment (MDDC-145) was written probably in 1945 (no date is attached to the manuscript) and declassified in July 1946 (Brues, Lisco, and M. Finkel 1946).^(a) Some of the results were included in summary form in the special issue of *Radiology* published in 1947 (Lisco, Finkel, and Brues 1947).

There were 3,090 mice in an experiment with ^{90}Sr . Half received single doses ranging from 0.05 to 5 $\mu\text{Ci/g}$, while half received monthly injections ranging from 0.01 to 1 $\mu\text{Ci/g}$ each month. (About 80% of the injected strontium is lost between injections.) The route of injection is not specified. It was probably intramuscular. The mice were about equally divided between Carworth CF1 strain and ABC hybrid mice. In addition, Sprague-Dawley rats and a few rabbits and dogs were introduced for species comparison.

The first finding was that radiostrontium can be a very potent carcinogen to bone in sufficient concentration. This was noted in mice injected by C. L. Prosser in an initial group of animals done 850 days before the preparation of the first report. Lymphoma incidence was not demonstrably increased, although some of the animals showed a blood picture suggestive of leukemia. Mammary tumors were in low incidence in the animals receiving strontium. Metastases of the bone tumors were numerous, especially in the rats.

Noncancerous changes seen after ^{90}Sr were greying of the hair in pigmented mice receiving over 1 $\mu\text{Ci/g}$ and the usual leukopenia, lymphopenia, and hypochromic anemia.

Cerium-praseodymium deposits to a considerable extent in liver, as described earlier. These animals showed both bone tumors and marked changes in liver, e.g., complete atrophy (except along the lower margin), ascites, and jaundice.

Finally, rats were fed ^{91}Y by stomach tube to determine effects of a largely unabsorbed element in the fission product group. Report MDDC-145 states that the LD_{50} for a single feeding in the rat is 20 mCi/kilo (i.e., 20 $\mu\text{Ci/g}$), a factor of five to ten above the corresponding parenteral doses of fission products. In a somewhat more detailed report, Lisco et al. (1947) reported carcinoma of the colon in rats receiving the large single feeding. A second group given seventy-eight feedings of 0.06, 0.20, or 0.46 mC of ^{91}Y over a three-month period did reasonably well, except for superficial ulcerative lesions of the colon, which were eventually serious enough to cause death.

It seems very likely that these reports are among the very earliest ones to prove the carcinogenic potency of the fission products. They were the first wave of a long series of large experiments at Argonne with small rodents, using a variety of beta- and beta-gamma-, as well as alpha-emitting radionuclides. (See subsequent sections and chapters.) They proved that the beta particle was not qualitatively different from alpha particles or gamma rays in inducing cancer in animals.^(b)

The extension of the work at Chicago under the aegis of the Argonne National Laboratory (ANL) will be considered separately from the work sponsored by the Manhattan Engineer District (MED) work concentrated upon in

(a) There were three individuals in the Chicago work with very similar names: R. D. Finkle, Miriam P. Finkel, and, as we saw in the chapter on radium, Asher J. Finkel. Where there is a chance of confusion, we will try to attach the appropriate initials.

(b) The probable mechanisms of the biological action of beta particles were discussed by Parker (1943).

this chapter. But it should be remembered that the groundwork was laid, the personnel and techniques already assembled, indeed some of the long-term experiments started by the middle and late-middle 1940s.

3. Transmission from Mother to Offspring

There was naturally a strong desire to know whether or not these new radioelements would produce greater or qualitatively different effects on the growing fetus as was fast becoming apparent in the work using external radiation sources. Also, it was important to know the extent to which they might pass the placenta or be secreted in the milk of lactating mothers. Miriam Finkel undertook such studies in the Met Lab Biology Division at Chicago. They were reported in the AEC literature and published relatively early (Finkel 1947).

Radiostrontium (^{89}Sr) was given intraperitoneally to prospective rat and mouse mothers and supplementary information obtained from one pregnant dog, which received ^{89}Sr intramuscularly.

The results were quite complex, partly because the interval between receipt of the dose and delivery seemed to make more difference than many other factors. But some generalizations can be made:

1. Strontium-89 passes readily from parent to offspring.
2. Doses of 2.5 or 5.0 $\mu\text{Ci/g}$ before conception reduced the number of litters.
3. Treatment during pregnancy using 5 or 10 $\mu\text{Ci/g}$ increased both the fraction of totally stillborn litters and the number of stillborn young in viable litters.
4. Uptake of ^{89}Sr by the fetus varies considerably during gestation. It is almost negligible up to the third quarter and is greatest during the last days of gestation.
5. Pregnant mothers receiving radiostrontium lived longer than nonpregnant animals. It is thought this reflects the fairly large portion of the dose that goes to the fetus rather than irradiating tissues of the mother. This would, of course, reduce the dose to the mother.
6. There is a higher specific activity in the newborn mouse than in the mother at the time of delivery.
7. Initial excretion of ^{89}Sr is much lower in very young mice than in adults.
8. Animals receiving doses in utero show retardation of growth, anemia, bone malformations, and, in a few instances, osteogenic sarcoma.

Although the results are all given in terms of activity units injected rather than radiation dose (as is true of all of Dr. Finkel's work), and thus comparison with external radiation sensitivity is not easy, the author makes the statement that "there is no indication that fetal and very young tissues are either more or less sensitive to Sr^{89} than are adult tissues" (M. P. Finkel 1947, p. 420).

4. Fission Products and Goldfish

Even before the interest in fisheries at the Hanford Site was generally known (see chapter 11), the Chicago group studied the accumulation and distribution of radiostrontium, barium-lanthanum, fission mixture, and sodium in goldfish. It is hard to believe that the motivation for this work represents anything more than that the Chicago people were good biologists and wanted some information on nonmammalian species of importance. However, we cannot be sure that the interest in fisheries in the Columbia River (chapter 11) did not provide a

stimulus in the highest managerial circles that was passed along in disguise to the Chicago workers.

Prosser et al. (1945) compared distribution after immersion of the fish in water containing the radioisotope with that after ingestion. They were comparable, indicating uptake through the gill and oral membranes. Calcareous tissues accumulated about 75% of radiostrontium and radiobarium with the rest residing early in soft tissues and being gradually transferred to bone. Lanthanum and a mixture of cerium, yttrium, and zirconium-columbium appeared to accumulate in visceral tissues, especially intestine. There was no fecal excretion of strontium after injection. Yolk of eggs in ripe ovaries took up some components of a fission product mixture, but not strontium or barium. The effect of age and calcium turnover appeared here as in mammals. Low calcium content of the surrounding water speeded uptake of ^{89}Sr and of fission product mixture.

Loss of the accumulated activity was quite slow when the fish were placed in inactive pond water.

Prosser, Hagen, and Grundhauser (1947) showed that solutions of stable barium, cerium, and bromine were toxic to goldfish at 1 ppm, 10 ppm, and 1,000 ppm, respectively, while strontium and iodine solutions seemed essentially nontoxic to goldfish. They also compared the lethality of x-irradiation, stable and radioactive elements in the alkaline-earth and rare-earth group but not in very much detail.

5. Enter the Dog and Some Comparisons

There was neither time nor space in the MED laboratories for the large and long-term dog experiments conducted in the postwar years (see later chapters). But the Chicago group did manage to inject a series of dogs with ^{89}Sr (and ^{239}Pu) as part of a much larger experiment using primarily external radiation. The initial published paper appeared in the Plutonium Project issue of *Radiology* (Vol. 49, No. 3) already cited. The paper, by Prosser et al. (1947), is something of a classic. Among other things, it shows in dogs and other large animals a faithful reproduction with the new radiation energies of the acute and subacute effects described as early as 1919 by Hall and Whipple (1919) and in Shields Warren's review (1942-1943) on the Pathology of Radiation (*Archives of Pathology*, Vols. 34, 35). The approach is considerably more physiological than in much of our more recent research.

The work with ^{89}Sr is mentioned briefly in the Prosser paper but in much more detail in a project report by Swift and Prosser (1947). Since this work has never been published in full form in the open literature (see NNES Hiatus, Appendix C), some details will be given here.

The injections were intramuscular, and the ^{89}Sr (with some ^{90}Sr contamination) from the Clinton Laboratories reactor was given in doses from 0.1 to 3.13 $\mu\text{Ci/g}$. The report does not give clear figures on the number of dogs used, but it was evidently enough for calculation of an LD_{50} .

The LD_{50} in 30 days was 1.0 $\mu\text{Ci/g}$ injected dose or 0.5 $\mu\text{Ci/g}$ retained dose. This is lower than reported for the rat and mouse by Anthony et al., or for the rabbit. Excretion was rapid in the mature dog^(a) as in rodents, with the bulk occurring in the first 3 days. After 10 days, excretion was quite slow. Therefore, the LD_{50} above based on retained dose might easily be based on retention after 10 days. But there was considerable variability in the longer-term retention with half-times from 1.6 to 37 days.

(a) Excretion was much slower and less complete in puppies and immature dogs.

As in the other species tested, deposition was primarily in bone. But the doses were high enough to produce acute damage before they were excreted, and the blood picture and general tissue pathology resembled, but did not duplicate completely, that seen after whole-body external radiation. The authors conclude that the initial dose is more important than the maintained dose. The main contrast in pathology to that of external radiation was the slower and less complete recovery of the leucocyte count due presumably to continued irradiation of bone marrow from the deposits in bone. There was not time for the development of long-term bone pathology. Nor was there time for a good analysis of long-term retention, but the data indicated power-function kinetics similar to those seen for radium (chapter 1).

The paper provides an opportunity for some interspecies comparisons with radiostrontium, as indicated in the tabular summary provided below:

Species	LD ₅₀ ³⁰ (Injected Dose Basis, $\mu\text{Ci/g}$)	LD ₅₀ ³⁰ (Retained Dose Basis, $\mu\text{Ci/g}$)	Excretion in 15 days, %
Mouse	7	2.8	60
Rat	5	2.5	50
Rabbit	5		90
Dog	1	0.5	58

The other reasons for the differences between dog and rodent obviously reside in factors other than retention and excretion.

This author has seen in abstract form a paper by Swift, Prosser, and Mika (1946) that presented a parallel study with ⁸⁹Sr in the goat. The rationale was to add a still larger mammal than the dog for extrapolation to humans and to check the tendency, suggested somewhat tentatively by the data shown above, that toxicity might increase with increasing body weight. The goat did not support this idea. The LD₅₀ in thirty days was in the range 1 to 1.5 $\mu\text{Ci/g}$, essentially the same as for the dog. Thus, a simple relation between acute toxicity and body weight did not materialize. In other respects, including response to whole-body x-irradiation, the goat resembled the dog. The decrease in lymphocyte count was noticeably less after ⁸⁹Sr in the goat than in the dog.

6. Chemistry and Radiocolloids

The enormous effort expended on establishing the chemistry, both physical and organic, of the fission products is quite beyond the scope of this book. A glimpse of the early processes is found in the letters quoted in the early parts of this chapter. The development of ion exchange resins was, of course, central to practical and large-scale separations. But the studies of metabolism were ringed by interest in how these elements attached to biomolecules and how their removal might be hastened.

Jack Schubert began such work at Chicago very early and has kept it as a career interest ever since. One of his early memos was seen through the courtesy of Dr. Hymer Friedell, and it gives the flavor of his advocacy for using exchange resins, either anion or cation, in preference to methods such as ultrafiltration, dialysis, and electrophoresis. In the memo, Schubert proposes a program for investigation of citrate and tartrate complexes of strontium and "at least one more rare earth" under physiological conditions. There were

undoubtedly many more such memos, but we will save discussion for the more extensive reports postwar.

These same avenues of investigation led Schubert to emphasize the radio-colloidal properties of fission products in solution (Schubert 1948). This is but a glimpse of a long-discussed and probably ubiquitous property of very dilute solutions that is especially notable with radiotracers. It can be characterized by diminished diffusion velocity, tendency not to pass membranes that are generally permeable to ions, adsorption upon glassware or walls of vessels, aggregation in solution, and even coagulation or peptization by electrolytes. Handling of solutions of radioisotopes at tracer levels can have a marked effect on the degree of colloid formation and undoubtedly has contributed in the past to many cases of nonreproducible results and effects attributed to "biological variability." We have already considered some of these phenomena in chapter 4.

Schubert's contribution in addition to presenting examples based on ultrafiltrability, ion exchange adsorption, and dialysis of carrier-free fission products of uranium is his characterization of radiocolloids and the very general role they play in tracer work whether in chemistry, physics, or biology. Note, for example, that a solution in radiocolloidal form may be distributed differently, at least initially, than an ionic solution because of the reaction of the RES to the "foreign object." The importance for nuclear medicine is obvious. This is highlighted in a paper by Gofman from Berkeley (1949). Further discussion will be reserved for later chapters.

C. The Chicago Toxicity Laboratory

The University of Chicago operated a toxicity laboratory during and after World War II which did numerous projects for the military.^(a)

The names of Kenneth DuBois, John Thompson, John Hutchins, and John Rust come immediately to mind as key members of the group. Their charge was largely chemical toxicology, and it ranged broadly. There was both official and unofficial liaison between this group and the MED and later ANL staff in the internal emitter field. Indeed, the Toxicity Laboratory was frequently studying the chemical toxicity of substances whose radioisotopes were under investigation at the Met Lab. Witness as one example the paper by Cochran et al. (1950) on acute toxicity of zirconium, columbium, strontium, lanthanum, cesium, tantalum, and yttrium.

D. Postlude at Chicago

While the end of World War II brought many changes to Chicago, the group most closely involved with work on fission products and actinide elements continued almost without missing a step. Indeed, several long-term experiments were already under way, which were fortunately carried forward pretty much as planned. Many of those in Met Lab administration returned to other duties, but, except for moving to the new facilities outside of Chicago, the progress of radioisotope research was relatively unbroken. It is tempting to launch into the extensions of fission product work immediately. But we need first to examine the MED work with the actinides and the genesis of the relative toxicity concept to make most efficient use of these later experiments and the philosophy behind them. Thus, further discussion will be postponed to chapter 8.

(a) Chemical Corps, U. S. Army for one.

V. Projects “Peppermint” and “Gabriel”

Early in the MED days, the MED and military planners were apprehensive that the Germans had learned the secrets of uranium fission, even if not the bomb, and might engage in air raids using radioactive isotopes as poisons. As early as September 15, 1942, J. C. Stearns wrote in a Met Lab monthly report on counter or defense measures including an elaborate selection of physicists at various educational institutions around the country who would be engaged to make radioactivity measurements in case of attack in their home locale (Stearns 1942). Note this was almost simultaneous with our first efforts to characterize the fission products from a biomedical point of view.

On a broader scale, selected military personnel in both the U.S. and U.K. forces were given radiation detection and measuring equipment and instructed in their use. Under the strictest kind of security, the fears of possible use of fission products for contamination of military or civilian installations were revealed to this relative handful of trusted individuals. Special shipments of the instruments were cached in various locations. Reports of any “epidemic disease of unknown etiology” were to be forwarded to specified officers with the plan that surveys for radioisotope contamination would be initiated thereupon. The same applied if unexpected darkening of photographic films appeared. Some of the instrument makers, e.g., Victoreen, developed and manufactured under high priority extra instruments to be placed in readiness. The Metallurgical Laboratory was a full partner, as well as the policy committee S-1 in Washington.

The American portion of this plan was code-named “Operation Peppermint” and was spearheaded by Major A. V. Peterson (1977) who writes about it in the Cave Brown-MacDonald book, *The Secret History of the Atomic Bomb* (1977).

While the American and British efforts were not officially combined, there was close liaison. Before the Normandy invasion, fears ran especially high that the Germans might be prepared to contaminate the beaches. Special efforts were made to inform General Eisenhower, and there were dry runs of Operation Peppermint by Headquarters, Chemical Warfare Service, European Theatre of Operations, U. S. Army.

None of this was very explicit about how biological doses would be estimated, etc. An effort to do this and to learn how to deal with such contamination was carried out, in part at least, at the University of Rochester Project. High-specific-activity short-lived radiosodium was sent by air from MIT to Rochester. It was applied to various surfaces in various configurations, and measurements were made. Then various procedures for removal were tried. From this, extrapolations were made to what the hazard might be had the emitter been mixed fission products. I am informed that this effort was named “Project Gabriel” (Bale 1979). It is likely that the above represents only a part of the effort.^(a)

(a) In addition to the probability of other measurements having been done elsewhere, there was one notable and quite unplanned result of this project. The ^{24}Na source prepared at MIT had an external radiation flux equivalent to about 5 g of ^{226}Ra . The rates were about 330 mr/hr at 1 m from the package. Such shipments usually went by military transportation. But there were problems in obtaining such at the time needed, and one of the commercial airlines agreed to carry it after briefing on where to stow it and how to handle it. Evidently all went well on the Boston-to-Syracuse leg of the trip, but because the box was to be off-loaded at the next stop, Rochester, it got moved to the forward compartment and very close to the pilot. On seeing the elaborate precautions taken by the University of Rochester crew when it was unloaded with

Neither of these involved sophisticated research. But they involved the same people and illustrate the variety of tasks that fell to the erstwhile laboratory scientists.

No evidence was ever found of the use of radioactive materials by the Germans, and the operations never needed to be activated. But they provided something of a prelude for later work at the Bikini and related tests in the Pacific. For the moment, we can put it beside the false alarm from thoriated toothpaste described in chapter 4.

VI. Work in Other U.S. Laboratories

We have concentrated on Berkeley and Chicago because, during the war, by far the bulk of true biomedical research on the fission products resided in these places. All of the installations handling fission products had to develop engineering controls and fairly elaborate systems for personnel protection and monitoring. Some of these efforts extended into possible environmental contamination and the effects of radioactive effluents on fish and wildlife and in agriculture. Notable among these was the work around the Hanford site, which will be discussed in chapter 11, along with later work at other production sites.

When the General Electric Company took over operation of the former Hanford Works, the biology operation began work on radioiodine. This had stood out as a biologically important potential contaminant from the large reactors and the separations plants. Details of the research results from this program and others will be taken up in chapter 8.

VII. Work in the United Kingdom

Cooperation with the British in sharing the scientific aspects of the development of nuclear energy has been amply documented. Near the end of the war, the Atomic Energy Research Establishment at Harwell could supply isotopes in the fission product series to medical researchers. Prominently interested in the biomedical implications was the group at Oxford, particularly Dame Janet M. Vaughan. (Dame Vaughan has continued actively in this field, especially with the bone seekers, ever since.)

Most of the publications are too late for the period covered by this chapter. But one which appeared in 1950 gives a vignette of their work. The study by Kidman, Tutt, and Vaughan (1950) was intended to determine the behavior of strontium as a function of diet and age in the rabbit. But the solutions of strontium isotopes contained varying proportions of ^{89}Sr , ^{90}Sr , and ^{90}Y . Thus, the radioactivity was constantly changing prior to and after injection. Yet, as stated

tongs, meters, etc., the pilot inquired into what it was. He was told enough to become thoroughly alarmed and insisted upon medical evaluation, for he had been, as he put it, "essentially sitting on that box!" This was July 6, 1943. Fortunately, it was a radioisotope that could be talked about without getting into classified areas; but why so much? The security people must have had some anxious moments.

It turned out that the pilot received less than 35 milliroentgens, and all medical examinations were negative. But this incident later played a prominent role in developing a guiding document for ICC regulations that were composed later with the help of a blue-ribbon committee of the National Research Council. (See Evans 1951.)

by the authors, "it seemed important, however, to obtain information about materials which are an immediate hazard, even though their estimation presented certain practical difficulties" (Kidman, Tutt, and Vaughan 1950, p. 210).

Despite the stated difficulties, the results agree well with those of the Hamilton et al. group at Berkeley and the work at Chicago: primary deposition in skeleton, rapid excretion initially, and difference in microdistribution of strontium and yttrium in bone. Excretion by both urinary and fecal routes was lower on a low-calcium diet than on a high-calcium diet. Uptake of strontium was always higher in animals on the low-calcium diet. Emphasized in the paper to a greater extent than in U.S. publications at the time is the hazard from the energetic ^{90}Y beta particles formed in bone from decay of ^{90}Sr .

VIII. Summary and Commentary

At the start of the Manhattan Project, the biomedical community faced an entirely new dimension in terms of the amounts of radioactivity to be expected if the uranium fission process worked. The total amount of radioactivity in all of the radium ever separated from its ores was but a tiny portion of that which could be expected in only a short time of operation of a nuclear reactor or from a fission bomb. Furthermore, hundreds of new isotopes could be expected. Fortunately, they were isomers of elements already known, but there were many unknowns, such as the fission yield, the many chains of radionuclides expected to be formed, and the like.

The new dimension was faced, even before the chain-reacting pile had been proven feasible. The cyclotrons at Berkeley (37 in. and 60 in.) could turn out fission products or mixtures in small quantities, and these were used early in the war years by Joseph G. Hamilton and his colleagues in tracer experiments with rats. The experiments were small, and the time between production of the radionuclides in the cyclotron and broad characterization of their behavior in the animal body was remarkably short. By the time fission products were available in quantity, their basic metabolic parameters had already been worked out. In addition to tracer work, the Berkeley group took time for some careful autoradiography, particularly of the bone seekers. They soon demonstrated significant differences in both micro- and macrodistributions among the elements produced in fission. There were those that behaved like calcium (e.g., strontium) and those that behaved like the rare earths.

There was also concern about those fission products that are gases or have gaseous phases in their decay scheme. A few crude experiments were tried, but the results will be reserved for discussion in chapters 9 and 10. There were also many calculations of possible lung dose from inhaled xenon and some interim standards set for airborne radioactivity in the installations of the MED.

At the Metallurgical Laboratory in Chicago, work with the fission products began slightly later than at Berkeley. As a result, they were able to secure amounts that permitted study of effects in small animals and of metabolism in large animals. The kinetics of retention and loss were emphasized. In addition, the fact that fission products could produce cancer, particularly in bone, as well as the entire galaxy of effects noted with acute external radiation doses became apparent. The initial carcinogenesis report is a classic, prepared by A. Brues, H. Lisco, and M. P. Finkel (1946).

There were also studies at Chicago on transfer of fission products from mother to offspring, considerable interest in the role of radiocolloids in

modifying or controlling behavior, including the contrast between carrier-free and ordinary fission products (J. Schubert and colleagues).

The fission products are, by and large, beta or beta-gamma emitters in contrast to the numerous alpha emitters we have dealt with in prior chapters. This is radiation of low linear energy transfer (LET) rate. As a result, the effectiveness per rad of deposited energy from the usual fission products is lower than that of radium, and there is a clear dose-rate effect. Thus, efficiency at low doses and low dose rates was found to be much lower than at high doses and high dose rates. Toward the end of the war, the Chicago group, especially M. P. Finkel, released data on the relative effectiveness of several fission products compared to radium. Under most circumstances, they were considerably less effective, but they became quite effective carcinogens at high doses and high dose rates.

Nearly all of the information on effects of fission products, during the war years, came from animal experiments. There were no exposures of humans, except for the rare accidental exposure and the early therapeutic trials of radio-nuclides like radioiodine. Only with the postwar exposures to fallout from weapons tests was there any appreciable exposure of either large groups of workers or the general population. These events will be discussed in chapter 12.

A part of the wartime effort on fission products was to prepare for the possibility of radiological warfare, e.g., by contamination of the landing areas for the invasion of Europe. After all, the fission process had been discovered in Germany. Why should they not be expected to pull a nasty surprise? Fortunately, the precautions taken were never needed, but the exercise has become part of the history we are reviewing.

In toto, the biomedical community was found ready for the new dimensions forced upon it by the enormous increase in amounts of radioactivity present or potentially releasable by the advent of nuclear fission. As in the decades before the war, it required development of new instrumentation and methodologies, and interaction of physics, chemistry, and biology. Only this time the barriers of security prevented the easy liaison of the 1930s. The biomedical community had to do much for itself under these circumstances, and it did.

References

- Anthony, D., K. Lathrop, and R. Finkle. Undated. *Radiotoxicity of injected Sr⁸⁹ for rats, mice, and rabbits. Part I. Introduction: Methods*. Metallurgical Laboratory report CH-3844, AEC report MDDC-1540, declassified October 1947.
- Anthony, D., K. Lathrop, and R. Finkle. 1947. *Radiotoxicity of injected Sr⁸⁹ for rats, mice, and rabbits. II. Metabolism and organ distribution*. Metallurgical Laboratory report CH-3846, AEC report MDDC-1363, declassified October 9, 1947.
- Anthony, D., K. Lathrop, and R. H. Snyder. 1946. *Radiotoxicity of injected Sr⁸⁹ for rats, mice, and rabbits. III. Lethal action and clinical changes*. Metallurgical Laboratory report CH-3845, AEC report MDDC-1364, June 1946, declassified October 17, 1947.
- Anthony, D. S. and R. H. Snyder. 1947. *Acute radiotoxicity of injected P³² in mice. I. Metabolism and survival*. AEC report MDDC-881, February 11, 1947, declassified April 30, 1947.
- Bale, W. F. 1979. Taped interview, Atlanta, Ga., November 6, 1979.
- Brown, A. C. and C. B. MacDonald, eds. 1977. *The secret history of the atomic bomb*. New York: The Dial Press/James Wade. [Especially the chapter by A. V. Peterson entitled "Peppermint."]
- Brues, A. M., H. Lisco, and M. Finkel. 1946. *Carcinogenic action of some substances which may be a problem in certain future industries*. AEC report MDDC-145, declassified July 31, 1946.

- Cochran, K. W., J. Doull, M. Mazur, and K. P. Du Bois. 1950. Acute toxicity of zirconium, columbium, strontium, lanthanum, cesium, tantalum, and yttrium. *Arch. Ind. Hyg. Occup. Med.* 1:637-50.
- Cohn, W. E. 1943. Letter to R. D. Finkle, dated December 22, 1943, declassified January 12, 1967.
- Durbin, P. W. 1976. What was going on at Crocker Laboratory when I landed there as a dishwasher and animal tender. Paper presented at the 21st Meeting of the Health Physics Society held in San Francisco, July 1976. [Typescript from tape and slides kindly supplied by R. L. Kathren, Richland, Wash.]
- Durbin, P. W. 1979. Personal interview October 31, 1979, San Diego.
- Evans, R. D. 1951. *Physical, biological, and administrative problems associated with the transport of radioactive substances*. NAS-NRC Publ. 205, Div. of Physical Sciences, Nuclear Science Series Report no. 11.
- Finkel, M. P. 1947. The transmission of radio-strontium and plutonium from mother to offspring in laboratory animals. *Physiol. Zool.* 20:405-21.
- Finkle, R. D., R. H. Snyder, and W. E. Kisieleski. 1947. *Acute radiotoxicity of (Ba-La)¹⁴⁰ in rats and mice. IV. Lethal action and clinical symptoms*. Metallurgical Laboratory report CH-3825, AEC report MDDC-1207, declassified June 27, 1947.
- Finkle, R., R. Snyder, and P. Tompkins. 1946. *Acute radiotoxicity of (Ba-La)¹⁴⁰ in rats and mice. I. Preparation and administration of the emitters*. Metallurgical Laboratory report CH-3828, AEC report MDDC-1248.
- Glasstone, S. 1950. *Sourcebook on atomic energy*, chapter 13. New York: D. Van Nostrand.
- Gofman, J. W. 1949. Studies with colloids containing radioisotopes of yttrium, zirconium, columbium, and lanthanum. I. The chemical principles and methods involved in preparation of colloids of yttrium, zirconium, columbium, and lanthanum. *J. Lab. Clin. Med.* 34:297-304. [Part II. E. L. Dobson, J. W. Gofman, H. B. Jones, L. S. Kelly, and L. A. Walker, AEC-2055 (1948). Also *J. Lab. Clin. Med.* 34:305-12 (1949).]
- Hall, C. C. and G. H. Whipple. 1919. Roentgen-ray intoxication: Disturbances in metabolism produced by deep massive doses of the hard roentgen rays. *Am. J. Med. Sci.* 157: 453-82.
- Hamilton, J. G. 1943a. Letter to C. M. Cooper, Metallurgical Laboratory, July 27, 1943, declassified November 15, 1967.
- Hamilton, J. G. 1943b. *Metabolism of fission products*. Monthly report of the Metallurgical Project, August 9, 1943, declassified May 19, 1947. CH-848. [See also CH-1049, October 1943, declassified February 1952.]
- Hamilton, J. G. 1944. *Metabolism of fission products*. Monthly report of the Metallurgical Project, April 25, 1944, declassified March 25, 1947. [No report number assigned.]
- Hamilton, J. G. 1945. *Tracer studies of fission product metabolism*. AEC report MDDC-1962, February 2, 1945, declassified June 1947.
- Hamilton, J. G. 1947. The metabolism of the fission products and the heaviest elements. Paper presented at the special symposium on the plutonium project at the 32d annual meeting of the Radiological Society of North America held in Chicago, December 1-6, 1946. *Radiology* 49:325-43.
- Hamilton, J. G. 1948. The metabolic properties of the fission products and actinide elements. *Rev. Mod. Phys.* 20:718-28.
- Hamilton, J. G. 1949. The metabolism of the radioactive elements created by nuclear fission. *New Engl. J. Med.* 240:863-70.
- Jacobson, L. O. 1946. *Acute radiotoxicity of (Ba-La)¹⁴⁰ in rats and mice. V. The effect of (Ba-La)¹⁴⁰ on the hematological constituents of the peripheral blood of rats and mice*. Metallurgical Laboratory report CH-3829, AEC report MDDC-1261.
- Jacobson, L. and R. Overstreet. 1945. The uptake by plants of plutonium and some products of nuclear fission adsorbed on soil colloids, BP-82. [Also published in *Soil Sci.* 65:129-34 (1948).]
- Jacobson, L. and R. Overstreet. 1947. A study of the mechanism of ion absorption by plant roots using radioactive elements. *Am. J. Botany* 34:415-20.

- Jones, D. C. and D. H. Copp. 1948. Studies of bone metabolism with the aid of radioactive strontium. UCRL-60. Univ. of Calif. Radiation Laboratory.
- Jones, D. C. and D. H. Copp. 1951. The metabolism of radioactive strontium in adult, young, and rachitic rats. *J. Biol. Chem.* 189:509-14.
- Kidman, B., M. L. Tutt, and J. M. Vaughan. 1950. The retention and excretion of radioactive strontium and yttrium (Sr^{89} , Sr^{90} and Y^{90}) in the healthy rabbit. *J. Pathol. Bacteriol.* 62:209-27.
- Kisielewski, W. 1980. Personal communication.
- Lapp, R. E. and H. L. Andrews. 1972. *Nuclear radiation physics*. 4th ed. Englewood Cliffs, N. J.: Prentice-Hall.
- Lisco, H., M. P. Finkel, and A. M. Brues. 1947. Carcinogenic properties of radioactive fission products and of plutonium. *Radiology* 49:361-63.
- Lisco, H. A., M. Brues, M. P. Finkel, and W. Grunderhauser. 1947. *Carcinoma in rats following the feeding of radioactive yttrium*. Metallurgical Laboratory report CH-3830.
- Metallurgical Laboratory. 1942. *Monthly report of the Metallurgical Project*. A. H. Compton, project leader. CH-259, September 15, 1942, declassified February 10, 1958.
- Metallurgical Laboratory. 1943a. *Monthly report of the Metallurgical Project*. A. H. Compton, project leader. CH-459, February 9, 1943, declassified March 12, 1952. [See also CH-498, February 1943, declassified March 1952, and CH-544, March 1943, declassified February 1953.]
- Metallurgical Laboratory. 1943b. *Monthly report of the Metallurgical Project*. A. H. Compton, project leader. CH-630, May 7, 1943, declassified December 4, 1958. [See also CH-1049, October 1943, declassified February 1952.]
- Metallurgical Laboratory. 1943c. *Monthly report of the Metallurgical Project*. A. H. Compton, project leader. August 9, 1943, declassified May 19, 1947. [No report number assigned.]
- Metallurgical Laboratory. 1945a. *Monthly report of the Metallurgical Project*. A. H. Compton, project leader. April 1945, declassified March 26, 1952. [No report number assigned.]
- Metallurgical Laboratory. 1945b. *Monthly report of the Metallurgical Project*. A. H. Compton, project leader. May 1945, declassified March 26, 1957. [No report number assigned.]
- Norris, W. P. 1978. Personal interview, Argonne, Ill., September 7, 1978.
- Parker, H. M. 1943. *Some physical aspects of the effects of beta radiation on tissue*. Metallurgical Project Health Division report CH-930, September 10, 1943, declassified February 28, 1950.
- Pecher, C. 1941. Biological investigations with radioactive calcium and strontium. *Proc. Soc. Exp. Biol. Med.* 46:86-91.
- Pecher, C. and J. Pecher. 1941. Radio-calcium and radio-strontium metabolism in pregnant mice. *Proc. Soc. Exp. Biol. Med.* 46:91-94.
- Peterson, A. V. 1977. Peppermint. Chapter in pt. III of Brown and MacDonald 1977, pp. 234-38.
- Prosser, C. L., C. W. Hagen, Jr., and W. Grundhauser. 1947. *The lethal action of x radiation, stable isotopes of fission elements, Sr^{89} , and $(\text{Ba-La})^{140}$ upon goldfish*. AEC report MDDC-1480, July 1947, declassified November 20, 1947.
- Prosser, C. L., E. E. Painter, H. Lisco, A. M. Brues, L. O. Jacobson, and M. N. Swift. 1947. The clinical sequence of physiological effects of ionizing radiation in animals. *Radiology* 49:299-313.
- Prosser, C. L., W. Pervinsek, J. Arnold, G. Svihla, and P. C. Thompkins. 1945. *Accumulation and distribution of radioactive strontium, barium-lanthanum, fission mixture and sodium in goldfish*. AEC report MDDC-496.
- Schubert, J. 1948. *The radiocolloidal properties of some fission products*. AEC report AECD-1910, February 11, 1948, declassified April 20, 1948.
- Scott, K. G., R. Overstreet, L. Jacobson, J. G. Hamilton, H. Fisher, J. Crowley, I. L. Chaikoff, C. Entenman, M. Fishler, A. J. Barber, and F. Loomis. 1947. *The metabolism of carrier-free fission products in the rat*. AEC report MDDC-1275, declassified 1947.

- Seaborg, G. 1977-1980. *History of the MET LAB Section C-1*. Four volumes prepared for Energy Research and Development Administration and numbered PQB 112, vol. I, 1977; vol. II, 1978; vol. III, 1979; vol. IV 1980. Univ. of Calif., Berkeley, Calif.: Lawrence Berkeley Laboratory.
- Seaborg, G. 1980. Personal interview at Berkeley, Calif., October 21, 1980.
- Simmons, E. L. and L. O. Jacobson. 1946. *Radiotoxicity of injected Sr^{89} for rats, mice and rabbits. IV. The hematological effects of enterally and parenterally administered strontium-89 in mammals*. Metallurgical Laboratory report CH-3797, AEC report MDDC-1387, August 1946, declassified October 8, 1947.
- Snyder, R. H., G. A. Sacher, and J. D. Teresi. 1946. *Acute radiotoxicity of $(Ba-La)^{140}$ for rats and mice. III. Effects on weight and food intake of animals treated with $(Ba-La)^{140}$* . Metallurgical Laboratory report CH-3832, AEC report MDDC-1343, June 1946, declassified September 15, 1947.
- Snyder, R. H., W. E. Kisielleski, D. S. Anthony, and R. D. Finkle. 1946. *Acute radiotoxicity of $(Ba-La)^{140}$ in rats and mice. II. Metabolism of $(Ba-La)^{140}$* . Metallurgical Laboratory report CH-3826, AEC report MDDC-1279, declassified September 10, 1947.
- Stearns, J. C. 1942. *Counter or defense measures*. In Metallurgical Project report for month ending September 15, 1942, declassified February 10, 1958.
- Swift, M. N. and C. L. Prosser. 1947. *The excretion, retention, distribution, and clinical effects of strontium-89 in the dog. I. Report of experimental work*. Metallurgical Laboratory report CH-3843, January 8, 1947, declassified October 9, 1947 as MDDC-1388. [There was also a statistical analysis of excretion and retention in individual dogs by G. Sacher, CH-3866, AECD-2108, June 1946, declassified July 1948.]
- Swift, M. N., C. L. Prosser, and E. S. Mika. 1946. *Effects of Sr^{89} and x radiation on goats*. U.S. Atomic Energy Commission report AECU-108, Metallurgical Laboratory report CH-3888, June 1946.
- Tompkins, P. C., A. Broido, and J. D. Teresi. 1946. *The handling of radioactive materials in the experimental biology section*. AEC report MDDC-377, January 4, 1946, declassified September 30, 1946.
- Warren, S. 1942-1943. Effects of radiation on normal tissues. Series of fifteen papers in *Arch. Pathol.* 34(2,3,4,5,6); 35(1,2) [under the heading "General Reviews"].
- Wassermann, R. H. and C. L. Comar. 1961. *Annotated bibliography of strontium and calcium metabolism in man and animals*. Washington, D.C.: U.S. Department of Agriculture, Agricultural Research Service.
- Way, K. and E. P. Wigner. 1948. The rate of decay of fission products. *Phys. Rev.* 73:1318-30.

OUTLINE
NEW DIMENSION NUMBER TWO—
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Capsule Chronology

- 1940** Neptunium-239 identified at Berkeley (McMillan and Abelson).
- February 1941** Plutonium-238, then known as 94^{238} , isolated at Berkeley from products of neptunium decay (Seaborg et al.).
- August 25, 1942** Entire world's supply of plutonium spilled and recovered from soggy copy of the Chicago Tribune (Met Lab, Chicago).
- September 10, 1942** First weighing of pure plutonium and thus of any synthetic element (Met Lab, Chicago).
- 1943** Biomedical groups working on fission products. Little activity with actinides.
- January 1944** Recommended that Joe Hamilton (Berkeley) receive 10 mg of plutonium for metabolic studies.
Seaborg cautions of physiological hazards of plutonium and requests safety equipment.
- February 1944** Hamilton reports that gut absorption of plutonium is poor, retention predominantly in skeleton, excretion small.
- 1944** Curium is synthesized by Met Lab group (Seaborg, James, and Ghiorso).
Large Met Lab report on metabolism of plutonium in rats.
- 1944–1950** Large comparative toxicity and pathology experiment at Rochester (Boyd, Fink). Comparison of polonium, radium, and plutonium. Published in 1950.
- 1945** Americium synthesized by Met Lab group (Seaborg, James, Morgan, Ghiorso).
Work with plutonium in animals begins at Chicago using mouse, rat, and dog. First work aimed at determining effects as well as metabolism. (As with the fission products, the Berkeley work is largely at tracer levels.)
- 1945–1946** Eighteen patients injected with plutonium—California (3), Chicago (3), Oak Ridge (1) and Rochester (11). Metabolic studies show man similar to experimental animals. Patients reviewed in 1971–1972 (Durbin at Berkeley); public announcement not made until 1976 (AEC, ERDA).^(a)
- 1945–1949** Bioassay work booms at Los Alamos.
- 1946** Chicago work shows details of distribution and excretion of plutonium.
- 1946** Extensive study of acute and subacute clinical effects of plutonium in the dog (Painter et al. at Chicago).
Effects of plutonium on tissue metabolism (Barron at Chicago).
Carcinogenicity of plutonium to bone of rodents described (Brues et al. at Chicago).
Los Alamos begins limited animal program to back up bioassay work in man (Langham).

(a) For abbreviations and acronyms, see Appendix D.

- 1946-1948** Autoradiography work at Berkeley underlines both macro- and microdifferences in distribution of plutonium in bone compared to strontium, calcium, and radium.
- 1947** Large report from Berkeley on effects of diet, valence state, complexing agents, etc., on behavior of plutonium in vivo (Van Middlesworth).
- Large differences noted between plutonium and the fission products ^{89}Sr and ^{90}Y .
- Chicago emphasizes "The Liver Problem" with plutonium. Differences between results at Berkeley and Chicago noted and mechanisms tackled.
- M. Finkel (Chicago) studies transfer of plutonium from mother to offspring.
- M. Finkel (Chicago) expands long-term pathology and comparative toxicity experiment with mice.
- Histopathologic effects summarized by Bloom (Chicago).
- 1947-1948** Open literature publications of Berkeley work on plutonium, also transplutronics (Hamilton; Scott et al.).
- 1947 et seq.** Possible uses of plutonium and transplutronics as heat sources considered.
- 1949** Use of comparative toxicity data at Tri-Partite Conference (see chapter 16).
- 1949** Berkeley workers publish work on metabolism of ^{242}Cm (Scott et al.).
- 1950** Publication of "Langham Equation" for plutonium excretion by man. Much discussion of bioassay methods and results (Langham at Los Alamos).
- 1950** Publication of Rochester work with polonium, plutonium, and radium as a monograph in the National Nuclear Energy Series. (*Biological Studies with Polonium, Radium, and Plutonium* — Fink.)
- 1951** Some of the Chicago biomedical work on plutonium published in National Nuclear Energy Series (*Industrial Medicine on the Plutonium Project* — Stone).

Chapter 7

New Dimension Number Two— Plutonium and the Transplutonic Elements (the Actinides); 1940–1950

Overview

This chapter addresses the second “new dimension” facing the biomedical community, especially the Manhattan Engineer District (MED) medical section and the laboratories associated therewith. This second new dimension was, of course, the synthesis of plutonium and its production in large quantities and, to a lesser degree, the other actinide elements isolated later. The first new dimension, the fission products, was as much the expectation of enormously increased quantities as *de novo* encounters. There was at least background information on the chemistry and biochemistry of many of the elements in their stable form. With plutonium and related elements it was essentially a “start from scratch” on all aspects.

Four laboratories contributed the bulk of the information needed: the University of California at Berkeley and the University of Chicago groups working as part of the Metallurgical Laboratory and Plutonium Project; the project at the University of Rochester Medical Center, which operated under the MED but was not part of the Metallurgical Laboratory or the Plutonium Project; and the Los Alamos Scientific Laboratory, which entered the arena of biomedical research in the late war years.

Emphasis here is placed on the work done during World War II. Only when immediate postwar findings helped enormously to answer some burning question do we stray briefly beyond the war years. An exception is war work that was published postwar. As in previous chapters, we review some of the unpublished work in more detail than some others of equal merit.

Inhalation studies are reserved for chapter 9, bearing of the data on standard setting for chapter 16, and environmental aspects for the special series of chapters on environmental contamination (chapters 11–15).

It will be obvious that the discernment and foresight of a relative handful of individuals played a key role in seeing that this work was done and that it was applied to operations promptly and in depth.

It will be noted that only U.S. work is cited. For the period under scrutiny, plutonium and the higher actinides were essentially an American monopoly.

I. The Problem

The new dimension introduced by the fission products involved delineating the properties of a great variety of radioisotopes. Some of them were isotopes of well-known elements; others had been studied very little. But the presence of radioisotopes of these latter actually made investigation of their biomedical behavior considerably easier than when there were only small quantities of stable isotopes to be handled by chemical methods. While there was much newness, the chief concerns centered on the tremendous quantities to be expected. In contrast, the new dimension brought about by the synthetic actinide elements was completely a foray into the unknown.

The "discovery"^(a) of plutonium by the Berkeley group posed exploration of absolutely virgin territory in chemistry, physics, biology, and medicine. When the relatively easy fission of the isotope ^{239}Pu was demonstrated, and the decision was made to try to produce it in kilogram quantities, there was some of the same apprehension regarding health hazards as we saw with the fission products. Biomedical behavior needed to be known as soon as possible. Glenn Seaborg seems to have had more concern for biomedical problems than did many physical scientists of the day. Perhaps that is because he was a chemist. (Chemists get interested in biochemistry and thus in biology.) Perhaps he was nagged by Joe Hamilton, who had to stand by and see the Crocker Laboratory's 60-in. cyclotron and the machine at Washington University, St. Louis, grind away at producing enough plutonium to be weighed and its chemical properties determined at Chicago without getting a single microgram for biological study.

Seaborg put it this way in retrospect: "Up to the fall of 1943 the cyclotron-produced plutonium in existence amounted to only 2 mg, a quantity distributed throughout the program over a period of one and a half years—and a quantity so precious we could not afford to ingest any of it" (Seaborg 1970).^(b)

About the time the Clinton pile was ready to produce plutonium and the Hanford project was under construction, Seaborg sent the following letter, quoted by Langham and Healy (1973), to the Medical Director of the Plutonium Project, Dr. R. S. Stone:

R. S. Stone

January 5, 1944

G. T. Seaborg

(Declassified July 18, 1969)

Physiological Hazards of Working with Plutonium

It has occurred to me that the physiological hazards of working with plutonium and its compounds may be very great. Due to its alpha radiation and long life it may be that the permanent location in the body of even very small amounts, say one milligram or less, may be very harmful. The ingestion of such extraordinarily small amounts as some few tens of micrograms might be unpleasant, if it locates

(a) It was not really a "discovery," for plutonium was known to exist in 1941-1942, although not by that name (Seaborg 1980). It was a synthesis of a manmade element. In recent years, it has been decided that minute quantities of plutonium do exist and have existed in nature, the result probably of uranium fission by the ambient neutron flux. But in 1941, plutonium was completely new and completely synthetic.

(b) While there was certainly no carelessness, it might be remarked that even in those early days there were spills, and thus opportunities for ingestion or inhalation, e.g., a broken centrifuge tube that required wiping up a large fraction of the world's supply of plutonium from the floor, or, in another case, recovering a spill from the Sunday edition of the Chicago Tribune (Werner in Seaborg 1972; Perlman in Seaborg 1972).

itself in a permanent position. In the handling of the relatively large amounts soon to begin here and at Site Y, there are many conceivable methods by which amounts of this order might be taken in unless the greatest care is exercised.

In addition to helping to set up safety measures in handling so as to prevent the occurrence of such accidents, I would like to suggest that a program to trace the course of plutonium in the body be initiated as soon as possible. In my opinion such a program should have the very highest priority.

GTS:EES

G. T. S. (signed)

c/c to S. K. Allison

A. H. Compton

T. R. Hogness

Central Reading File

(Seaborg 1944)

By January 19, 1944, it was recommended that 10 mg of plutonium for metabolic studies be made available to Dr. J. G. Hamilton "as soon as possible." By January 29, 11 mg of plutonium were allocated, shipped about February 1, and delivered to Dr. Hamilton on February 10. The Metallurgical Laboratory's monthly report for February (!) of that year (Allison 1944) carried the following from Dr. Hamilton:

Product Studies—Oral absorption of all valence states is less than 0.05%; lung retention high; absorbed material predominantly in the skeleton; excretion very small in urine and feces. (Langham and Healy 1973, p. 574)

This set the stage. The new element was biomedically similar to radium. The story of the radium dial workers, patients, chemists, and others had made a deep impression on Hamilton, on Seaborg, and on Stone. Laboratory modifications were instituted immediately, and the plant designs and working plans were adjusted to the philosophy that plutonium would be a very hazardous substance indeed.

Naturally, a full biomedical study was considered essential, and the Manhattan Engineer District (MED) faced up to the second major new dimension in its biomedical program. The work received added impetus as americium and curium were synthesized in 1946 and 1947, particularly since it was found that these were produced by successive neutron reactions in ^{239}Pu in the chain-reacting pile and in the products of some nuclear detonations. Thus, they would be present when fuel was reprocessed and in the debris from weapons. The quantities were far less than those of plutonium or fission products, but their very presence dictated more biomedical research.

The balance of this chapter considers, after a preliminary review of the actinide series of elements, the biomedical research done during World War II on these new elements, especially plutonium. The following chapter will tackle the enormous postwar research programs with both the fission products and the actinide elements.

II. The Actinide Elements

Just as we had to pause briefly in chapter 6 to review the production and properties of the fission products, we must pause here to review a few salient facts about the history and properties of the actinide elements.

The categorization "actinide elements" came out of the synthesis and properties of plutonium, neptunium, americium, curium, and later elements. Two

books by Seaborg present the essence of the story in clear-cut prose and fascinating style (Seaborg 1963, 1972). Full details can be found in some of the National Nuclear Energy Series (NNEs) and other volumes (Seaborg and Katz 1949; Seaborg, Katz, and Manning 1949) and in papers published along the way (Seaborg 1945, 1946.)

The search for transuranium elements in the late 1930s was based on the prewar periodic table (figure 7.1). Properties of the elements, when prepared, were expected to be like their nearest relatives in the table. For example, element 93 was expected to have properties like rhenium; 94 was expected to be like osmium, etc. This led to many unproductive investigations, complicated by the fact that in much of the early work the products of neutron bombardment of uranium were not transuranium elements at all, but fission products. The realization of this error came in the late thirties. With the establishment of the facts of uranium fission in 1939, the work took a different tack, and ^{239}Np ($^{239}_{93}\text{Np}$) was identified in 1940 in work at the 60-in. cyclotron in Berkeley. This was the first true transuranium element to be synthesized and characterized. Its properties were not at all like rhenium or technetium, even though they were in the same column of the old periodic table.

																								He	
H																									
Li		Be																B		C	N	O	F	Ne	
Na		Mg																Al		Si	P	S	Cl	Ar	
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr								
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe								
Cs	Ba	La-Lu	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn								
Fr	Ra	Ac	Th	Pa	U	93	94	95	96	97	98	99	100												
		La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu									

FIGURE 7.1. Periodic table of the elements as it existed at the beginning of the work on the new heavy elements. (Redrawn from Seaborg 1963, p. 38. Reprinted with permission of Prentice-Hall, Inc., Englewood Cliffs, New Jersey, copyright 1963.)

In late 1940, McMillan, Kennedy, Wahl, and Seaborg prepared another isotope of neptunium, ^{238}Np . This decayed by β^- emission to what appeared to be element 94, weight 238. On the night of February 23, 1941, the Berkeley group succeeded in separating the new element known then as 94^{238} and now as ^{238}Pu . Note that the first synthesis produced ^{238}Pu , not the more fissionable ^{239}Pu . The 239 isotope was searched for as a decay product of ^{239}Np . This was successful, again at the Crocker 60-in. cyclotron a little later, in the spring of 1941 (Seaborg et al. 1946). The first experiment with weighable (and barely visible) amounts of plutonium was carried out by Burriss Cunningham in collaboration with Michael Cefola and Louis Werner using the new and very clever techniques of ultra-microchemistry (Cunningham in Seaborg 1972). The fission cross section, fully

50% greater than the other most likely fissile material, ^{235}U , was established with slowed neutron beams from the 37-in. cyclotron. Again, the properties of the new element 94 were not at all like those of its relatives in the old periodic table, osmium or ruthenium.

Skipping a multitude of intermediate steps, in thought and deed, let it be said that Seaborg and the Berkeley group decided that these new elements belonged in a series analogous to the lanthanides, but one that began with actinium, and hence should be called "The Actinide Series." As the work progressed and larger quantities were available, the chemists at the Met Laboratory in Chicago (where Seaborg spent the war years)^(a) confirmed fully the progression of properties and predictions of behavior based on such a series. Thus, the elements we are interested in for this chapter became known as part of the actinide series of elements, or commonly the actinide elements.^(b) Analogies were drawn where appropriate, not to the old periodic table, but to the already established lanthanide series or rare earths. Soon the periodic table was rewritten by the Seaborg group as shown in figure 7.2.

1																	2				
H																	He				
3	4															5	6	7	8	9	10
Li	Be															B	C	N	O	F	Ne
11	12															13	14	15	16	17	18
Na	Mg															Al	Si	P	S	Cl	Ar
19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36				
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr				
37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54				
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe				
55	56	57-71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86				
Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn				
87	88	89-103	(104)	(105)	(106)	(107)	(108)	(109)	(110)	(111)	(112)	(113)	(114)	(115)	(116)	(117)	(118)				
Fr	Ra	Ac																			
		LANTHANIDE SERIES	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71				
			La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu				
		ACTINIDE SERIES	89	90	91	92	93	94	95	96	97	98	99	100	101	102	103				
			Ac	Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	Lw					

FIGURE 7.2. Periodic table of the elements as it was rewritten by the Seaborg group in the 1940s to show the new actinide series. (Redrawn from Seaborg 1963, p. 41. Reprinted with permission of Prentice-Hall, Inc., Englewood Cliffs, New Jersey, copyright 1963.)

The synthesis and isolation of americium and curium came at the wartime Metallurgical Laboratory in Chicago after the big push to develop the methods for isolation and extraction of plutonium on an industrial scale was over. A. Ghiorso, R. A. James, L. O. Morgan, and G. T. Seaborg were involved in this

(a) Seaborg 1980.

(b) The early members, including thorium and uranium, although officially part of the series, are not so commonly identified as "actinides," and we have considered these separately in earlier chapters of this book because of their natural occurrence in quantity.

work. For curium, the cyclotron at Berkeley did the bombarding, while the chemical separations went on at Chicago. Curium-242 was separated in the summer of 1944 after bombardment of ^{239}Pu with 32-MeV helium ions. Americium-241 was isolated at Chicago in 1945 after bombardment of ^{239}Pu with neutrons in a reactor. Both of these elements fitted well the scheme of the actinide series. As Seaborg remarked, "...the actinide concept had crystallized" (Seaborg 1972, p. 57). (See also Seaborg 1949a,b; Seaborg, Katz, and Manning 1949; Seaborg, James, and Morgan 1949; Seaborg, James, and Ghiorso 1949.)

The actinide concept was not only useful to the chemists; it was useful also to the biochemists and biologists in working out the metabolic behavior of this group of elements. The literature is voluminous, but the writings of David Taylor (Royal Cancer Hospital, Sutton, Surrey, Great Britain, now at the Karlsruhe Institute in Germany) are especially useful in depicting the chemical properties of importance to biological behavior of both plutonium and the transplutonium elements (Taylor 1973a,b).

All of the actinides above actinium are radioactive, except that thorium and uranium in their natural state are quite weakly radioactive (chapters 2 and 4). For our purposes, it is primarily the deposition of energy from ionizing radiations (alpha, beta, and/or gamma) that governs the biological effects of importance for the higher actinides, although some component of chemical toxicity cannot be ruled out completely.

III. The Metabolism of Plutonium

A. Radiochemical Studies In Animals

The Metallurgical Laboratory's monthly report for the period ending October 15, 1944 (Hamilton 1944)^(a) discusses in some detail the facts from Berkeley in the cryptic announcement made in February. Organ distribution and retention in rats are given at four, sixteen, and sixty-four days following oral, intramuscular, intravenous, subcutaneous, and intrapulmonary administration. The doses were 15 μ (15 μg) per animal, with three rats in each group, the same protocol as in the research with fission products.

The skeleton is emphasized as the chief organ of deposition and the digestive tract the principal channel of excretion. Retention in the skeleton was tenacious, with the half-period estimated at over six months.

Absorption in the gastrointestinal tract was about 0.05%, considerably less than the absorption of radium. Valence state played an important role in absorption. More complete information is found in a large Met Lab in-house report (Scott et al. 1944) which appeared, in part, in the *Journal of Biological Chemistry* (Scott et al. 1948a).

Liver had the highest concentration among the soft tissues. There was a marked effect of valence state. Deposition in liver after intravenous administration was greatest for +4 plutonium, intermediate for +3 plutonium, and least for the +6 state. This was essentially the reverse of the effect of valence state on

(a) The plutonium used at Berkeley for biomedical work did not come from the 60-in. cyclotron, which produced relatively small amounts of the ^{239}Pu isotope. Instead, Berkeley, like Chicago, Los Alamos, and Rochester, used ^{239}Pu produced in a nuclear reactor, at first the Clinton Laboratory reactor (Oak Ridge).

absorption from the gut. The liver was not so high after administration by other routes. Kidney and spleen were the next highest among the soft tissues.

Even in the early studies, there was considerable interest in finding mechanisms to explain the kinetics found. Lester Van Middlesworth prepared a Ph.D. thesis, subsequently issued as a Manhattan District declassified report (Van Middlesworth 1947) that brought many influences to bear, such as diet, valence state, complexing agents, etc. Some of the most pertinent findings are outlined below and in figure 7.3.

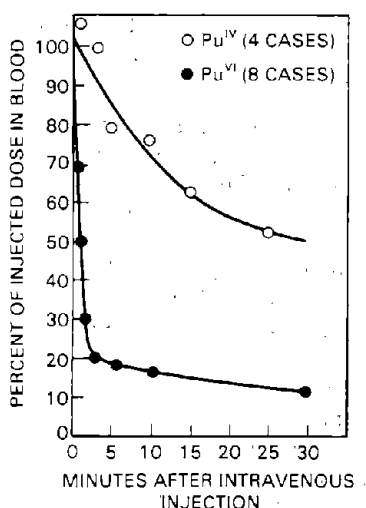


FIGURE 7.3. Effect of valence state on disappearance of plutonium from the blood of rats following intravenous administration. (Redrawn from Van Middlesworth 1947.)

1. By a clever selection of radiation types and energies, the behavior of ^{239}Pu , ^{89}Sr , and ^{88}Y could be distinguished in the same animal (in this case rats).
2. Severe phosphate deficiency greatly reduced the retention of strontium. The retention of plutonium was somewhat reduced, but tissue distribution remained the same.
3. Excretion patterns of the three elements were quite different, although all three reached a very low rate within a few days after injection. Urinary excretion of plutonium was very slow after the first week, so that less than 4% of the administered dose appeared in urine over an eleven-week period. Fecal excretion was much higher and continued to be quite significant over the eleven weeks (cumulative about 25% of administered dose). In fact, the rate of excretion of plutonium in feces, while initially lower than the rate with either strontium or yttrium, exceeded either of these after the fifth week.
4. Scurvy, which produces changes in connective tissue and bone osteoid matrix, had no significant effect on the distribution of plutonium.
5. The tissue distribution of plutonium was not altered by three weeks of a protein-free diet, although retention at the injection site was reduced.
6. The valence state +4 ($\text{Pu}(\text{IV})$) was retained at a site of intramuscular injection longer than the +6 state ($\text{Pu}(\text{VI})$). Distribution was unchanged.

7. Valence state had a marked effect on disappearance from the blood (figure 7.3). It was postulated that this difference, plus the much larger proportion of the +4 state depositing in liver, confirmed the idea that the (Pu[IV]) may be in a colloidal state.
8. Maximum uptake of plutonium (and yttrium) in a fracture callus occurred on the second or third day, whereas strontium deposition did not begin until the period of most active calcification.
9. Methionine supplements in the diet produced a moderate decrease in deposition of plutonium in the skeleton when it was injected in the valence VI state, whereas large doses of cysteine injected one hour before intramuscular injection had no effect on absorption of (Pu[IV]) but reduced both absorption and skeletal deposition of (Pu[VI]).

All of these findings bear on a primary problem that was in the minds of the early workers and continued well into the postwar years. What is the chemical form of plutonium in tissues and excreta? Can the knowledge of the chemistry aid in deriving means for therapeutic removal of plutonium? We will return to these questions.

Let us turn first, however, to the published summaries of the Berkeley work already cited in connection with the fission products (Hamilton 1947, 1948). Figure 7.4, taken from Hamilton's 1947 paper, shows the uptake and retention in bone of several actinides, including plutonium, following parenteral administration. Note the almost negligible loss from bone over a period of sixty-four days and contrast this with the fission products discussed in chapter 6, where loss, while slow, was clearly at least measurable, except for element 61 (figure 6.2).

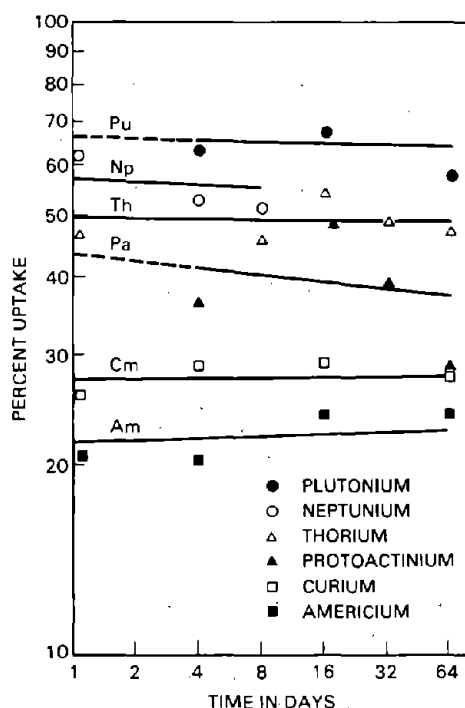


FIGURE 7.4. Uptake and retention of actinide-type elements by bone of rats. (Redrawn from Hamilton 1947. Reprinted with permission of Radiological Society of North America, Oak Brook, Illinois, copyright 1947.)

Figure 7.5, also from the Hamilton review, shows uptake and retention of these same actinides by liver. The contrast in retention between bone and liver is even more marked than in the case of the fission products. The difference is due largely to the avid retention in bone.

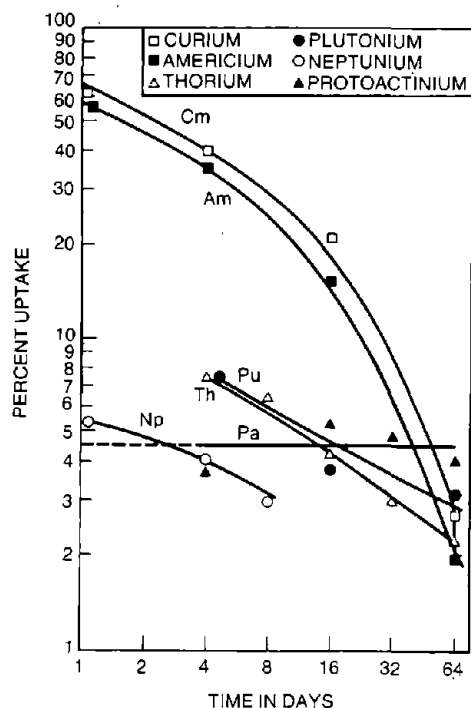


FIGURE 7.5. Uptake and retention of actinide-type elements in liver of rats. (Redrawn from Hamilton 1947. Reprinted with permission of Radiological Society of North America, Oak Brook, Illinois, copyright 1947.)

Work at Chicago on the metabolism of plutonium followed much more closely on the heels of the work at Berkeley than was the case for the fission products. One of the earlier reports concerned metabolism in and effects on a dog (Cole and Prosser 1945). The injection was intravenous. The findings were similar to those reported from Berkeley in the rat, but, in addition, combination of product (plutonium) with blood plasma proteins was described along with mention of high concentrations in lymph nodes and high specific activity in spleen. The plutonium was given in the +6 valence state.

In the same report (and without any indication in the table of contents), some metabolism figures are also given for mice. Besides the now familiar findings, they took autoradiographs of the liver of mice treated intraperitoneally and found very little of the product on the outer linings. This fact was taken as proof that the liver deposition was from complexes in blood plasma.

Another in-house report from Chicago appeared as part of a conference on plutonium held May 14-15, 1945 and issued as a Met Laboratory report on July 23, 1945 (Nickson 1945). A paper by R. D. Finkle in that volume gives summary data on the dog and mouse using plutonyl (+6) nitrate by intravenous, intraperitoneal, and intramuscular routes of injection but without much analysis of the findings.

By far the most complete in-house report from Chicago was issued in May 1947 (though dated August 1946) with contributions from most of those concerned with the metabolic studies (R. D. Finkle et al. 1947). This report was

scheduled for publication as a detailed paper in the *Plutonium Project Record* (PPR), later the NNES, Volume 22G, which did not get published (See NNES Hiatus, Appendix C). Because of its summary nature and the presence of constant demand, it was reworked by Francis E. Throw, editor for the Radiological and Environmental Research Division, Argonne National Laboratory and reissued in March 1976. The chapter on metabolism was prepared by Snyder, Kisielewski, and R. D. Finkle. The abstract is presented below.

Abstract. The most important aspect of plutonium metabolism is the affinity shown by the bone to capture the material and hold it for a long time. From data on rats that received plutonyl citrate and those that received plutonyl nitrate, it was estimated that the half-time for the plutonium in the skeleton was roughly 1.5 yr. With rats and mice, over 50% of the administered (intravenous) plutonium was deposited in the skeleton.

At 200 days, deposition in the rat skeleton averaged 10% of the retained dose per gram of bone ash. Somewhat higher concentrations were found in the lumbar and thoracic sections of the spine, while lower concentrations were found in the skull, jawbones, and ribs.

The next largest deposit of plutonium was in the liver (20 to 40%). This organ did not hold the material; the concentration was reduced to approximately one-tenth of the initial value within 200 days. In mice, part of the plutonium that left the liver found its way to the skeleton; but in rats no evidence of such a relocation was observed. The removal from the liver offered that the first step is a conversion of the plutonium from one molecular form to another form, more easily removable from the liver. The suggestion that the collection of a large fraction of the plutonium by the liver is an abnormality associated with intravenous administration was not supported by the evidence presented. Intramuscular and intraperitoneal administration of plutonyl salts also produced high plutonium concentrations in the liver.

Intramuscular injection of plutonyl nitrate in mice resulted in slow absorption: 23% was absorbed in 4 days, and 46% in 64 days. Of the absorbed portion, 20% was found in the liver initially.

Rats that received plutonyl salts by vein excreted 17% of the dose in the first two weeks and another 10% in the next six weeks. Over this eight-week period, the feces contained three times as much plutonium as did the urine. The rate of excretion on the eighth week was 0.08%/day. Mice that received similar treatment excreted 12% in the first two weeks and another 12% in the next eight weeks. The rate of excretion in the tenth week was 0.07%/day.

(R. D. Finkle et al. 1947)

Note that the estimate for half-time in the skeleton has slipped up to 1.5 yr. Note also differences in the concentrations in different bones, not emphasized in the earlier reports. The analytical methods are carefully described. Recoveries were good for most tissues and feces, but poor for urine because of problems with spattering in the dry-ashing procedure, and also for overall recovery when much time elapsed between injection and termination of the experiment. The figures were $97\% \pm 3\%$ for soft tissues, $94\% \pm 3\%$ for feces, 75% for urine and 88% for overall recovery with a range from 70% to 100%. These low overall recoveries were attributed to plating out of plutonium from urine and feces on the metal metabolism cages.

Excretion was fairly regular except in the mouse, where it was quite variable. A picture of the general trend of excretion is shown in figure 7.6, taken from the subject report.

Note that the bulk of the excretion occurs in the rat in the first few days with not over 2% being excreted in the three- to fifty-day period. Urinary excretion

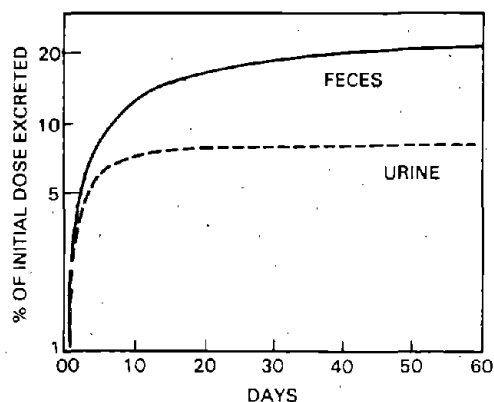


FIGURE 7.6. Mean accumulated excretion of plutonium in urine and feces of rats after parenteral administration. (Redrawn from Finkle et al. 1947.)

appears to go to zero after five to eight days, but is actually about 0.01% to 0.02%/day. The importance of this for bioassay procedures is obvious if the same applies to man (see chapter 16). Fecal excretion remained significant for at least forty days.

There are some contrasts in detail between these excretion figures and those of Van Middlesworth (1947), which are shown along with data for strontium and yttrium in figure 7.7.

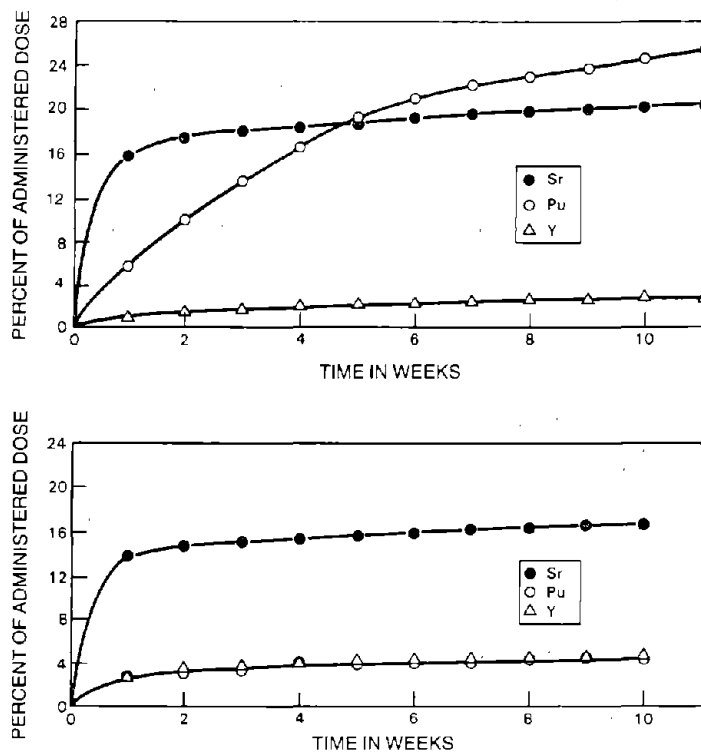


FIGURE 7.7. Cumulative excretion of plutonium, radiostrontium, and yttrium after parenteral administration (urine [A]; feces [B]). (Redrawn from Van Middlesworth 1947.)

The Chicago workers were especially impressed by the deposition in liver under various conditions. In the report by R. D. Finkle et al. (1947) there is a section called "The Liver Problem." They considered as a mechanism entrapment of colloidal material, even precipitated plutonium, brought about by rapid intravenous injection. Influence of valence state also suggested this since the more insoluble +4 valence state was "the worst offender." Would this apply to slow absorption from lung or wound site in man? Would the amount in liver be significant in man? Specific animal experiments were designed to investigate "the liver problem." It turned out that the route of administration was not a prime factor in determining liver deposition. Even attempts to obtain low liver content after intravenous administration by using the citrate complex, great care to remove foreign matter such as lint and dust from the injection solution, and use of highly acidic stock all failed to remove "the problem." Always the initial liver content exceeded 20% of the injected dose. As we will see later, the story is no different for humans.

The Berkeley group consistently got much less in liver than the Chicago workers. Two possible explanations were: (1) the amounts used by the Chicago group were much larger because they were interested in toxicity; and (2) while initially both laboratories used the same source of plutonium, in later work the sources were different.^(a)

The Chicago report concludes its discussion of "The Liver Problem" by pointing out a striking similarity in four of the larger intravenous experiments, where each curve seems to be composed of two separate lines in the plot of percent dose against time. This is reproduced here as figure 7.8. They argue that the rather sudden increase in release of plutonium from the liver represents the culmination of solubilization processes, probably several, and subsequent mobilization. Analyses of the plutonium content of the blood showed a rise at about the time of the inflection in the rate of loss from liver. Interestingly enough, rats receiving plutonium in the lungs failed to show the increase in rate of loss from liver at ten to twenty days. Many attempts were made to find what changes were occurring in the chemical state of plutonium in the liver, but,

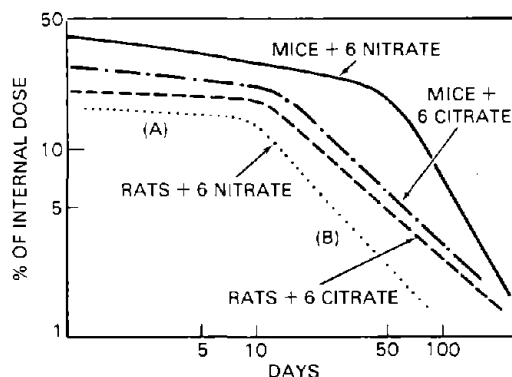


FIGURE 7.8. Retention of plutonium in various forms in the liver of rats and mice. (It is postulated that the portions marked "A" correspond to the period during which plutonium is being converted from the chemical form in which it is deposited to a more mobile form; part "B" is taken to show removal rates of this more transportable form of plutonium.) (Redrawn from Finkle et al. 1947.)

(a) The report indicates that this point is discussed further in another PPR report. But only an abstract has been obtained of this, which does not address the subject, although it points out the importance of the rate of injection.

except for finding that all of the intravenously injected plutonium was associated with protein, no specific explanation was forthcoming. Muntz and Barron (1947) had already implicated one of the heavier serum proteins.

It is puzzling that this phenomenon (i.e., a change in mobility) has not, so far as this author can find, been followed up in postwar work. It might be pertinent to means for therapeutic removal.^(a)

M. P. Finkel's work (1947) on transfer of radioelements from mother to offspring in laboratory animals, already discussed in chapter 6, was extended also to plutonium. Very little plutonium seemed to cross the placenta, in line with its general tendency toward insolubility. But, as with ^{89}Sr , the plutonium-treated mothers lived longer than the nonpregnant animals. Possibly enough plutonium leaves the mother via the milk to reduce her body burden. While the young at birth retained only a small portion of the plutonium in the mother, the young from mothers receiving ^{89}Sr had activities above those in the mother.

The newborn appeared to absorb much more plutonium from the gut than do adults—in line with findings with other substances. This was not sufficient, however, to bring about pathologic lesions over the period of the experiment as occurred with radiostrontium. Thus, the hazard of plutonium by placental transfer, or milk from lactating mothers, appears less marked than with fission products, despite the much higher biological effectiveness of the plutonium alpha particle. The mice in utero were kept for length-of-life studies, but no osteosarcomas appeared. This phenomenon deserves further investigation since, as we will see presently, plutonium is in general more effective at low doses than is strontium.

The effect of valence state on disappearance of plutonium from the blood, noted earlier in the work of Van Middlesworth (1947) at Berkeley, was also noted in the Chicago work along with the fact that complexing with citrate did not alter the metabolism of either plutonium or yttrium (Schubert et al. 1950).

Kisieleski and Woodruff (1947) looked at the effect of valence on absorption after intramuscular, subcutaneous, and intrapulmonary routes. The effect described was similar to that noted earlier when other routes of entry were utilized.

The Los Alamos Scientific Laboratory was, of course, a mecca for work in the physics and chemistry of plutonium. During the war years, its biomedical program was centered largely around the health care of the workers there and ways to estimate body content from measurement of excretion (bioassay). We will discuss this in more detail in chapter 16. The laboratory did not have facilities for a biomedical program with animals until toward the end of the war in Europe. Wright Langham, who was a central figure in the bioassay work, did persuade management to let him do some experimental work with rats, primarily aimed at checking out excretion phenomena that had not been explained and some tissue distribution work. This work was reported in May 1946 as a Los Alamos report and later issued as an Atomic Energy Commission (AEC) declassified report (Langham 1946). It gives a summary of much of the Berkeley and Chicago work as well as their new data. Parts were published in 1947 (Carritt et al. 1947).

(a) The "liver problem" per se has not disappeared. There are indications from many sources, including the Thorotrast work described in chapter 4, that liver damage may be significant under some conditions, and it cannot be neglected.

The new work emphasized further the growing suspicion that extrapolation from the rat to man is especially shaky in the area of bioassay.

Langham's work shows what may be an effect of dose size on the ratio of fecal to urinary excretion (F/U). At least table 5 of his paper shows a progressive increase at five days from an F/U ratio of 4.93 to 8.09 with increasing dose from 1.1 γ (μ g) to 15.0 γ . But at 52 γ , the ratio was back to 5.45. None of these may have application to the much lower doses involved in radiation protection work. Also, by thirty days the ratio seems to be quite constant (Carritt et al. 1947):

A key conclusion was that, regardless of valence state, distribution of plutonium slowly absorbed into the body by oral, intramuscular, or intrapulmonary routes was similar to that following intravenous injection.

Comment: These radiochemical studies during the war years at Berkeley, Chicago, and Los Alamos established the main features of plutonium metabolism in animals. While there were differences, the similarities in primary findings are striking, especially if it is remembered that security measures interfered with easy communication, and the methodologies were idiosyncratic.

Toward the end of the war years and immediately thereafter, there were publications showing the metabolism of americium (Scott et al. 1948b) and of curium (Scott, Axelrod, and Hamilton 1949). These fell clearly within the actinide group of elements in terms of general behavior, but there were differences between them and plutonium. We will reserve discussion of these for chapter 8.

B. Autoradiographic Studies

It is not clear whether the autoradiographic studies at Berkeley involving plutonium were simultaneous with or somewhat later than the work on fission products described in chapter 6. But the fact that microdistribution of plutonium was very different from that of radium rapidly became a central issue in guiding standard-setting.

Figure 7.9 is a combination photomicrograph and autoradiograph of an adult rat femur seventy days after injection of ^{226}Ra (Durbin 1976). The distribution in the mineral phase is much like that shown in chapter 6 for radiostrontium.



FIGURE 7.9. Photomicrograph (left) and autoradiograph (right) of an adult rat femur seventy days after injection of ^{226}Ra . Note the similarity of the radium deposition (autoradiograph) to the mineral phase seen in the photomicrograph. (Unpublished figure from Durbin 1976.)

In figures 7.10 and 7.11, we see photomicrographs and autoradiographs of adult rat femurs one week and eight weeks, respectively, after injection of plutonium (presumably ^{239}Pu).

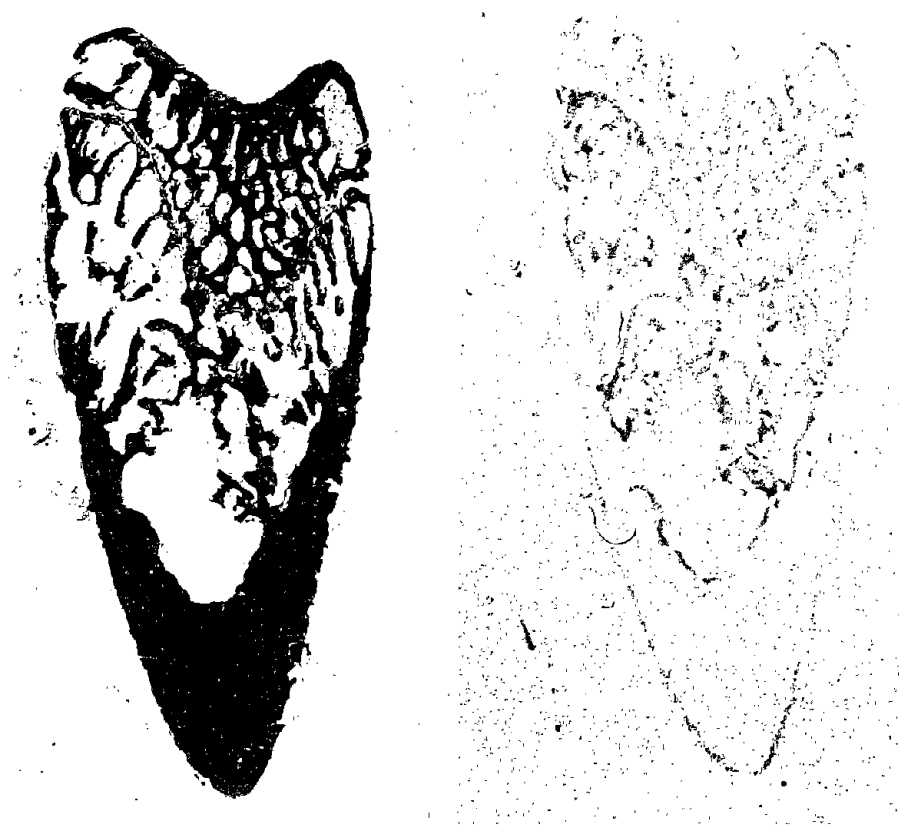


FIGURE 7.10. Photomicrograph (left) and autoradiograph (right) of femur from adult rat injected with plutonium and sacrificed one week later (note the superficial distribution of plutonium). (From Hamilton 1947. Reprinted with permission of Radiobiological Society of North America, Oak Brook, Illinois, copyright 1947.)

The difference between plutonium and radium is striking, as is the similarity between plutonium and some of the rare earths (Hamilton 1947). These autoradiographic studies led to the postulate that plutonium combined with the organic matrix of bone, while radium entered the mineral crystals (hydroxyapatite) by exchange for calcium. It became an important bench mark for explaining the differences in toxicity to be discussed later in this chapter. Van Middlesworth (1947) emphasizes the difference between strontium and plutonium (strontium being like radium as we saw in chapter 6). He attributes the localization of plutonium to deposition on the endosteal and periosteal surfaces—a more correct explanation than simply “binding with organic matrix.”

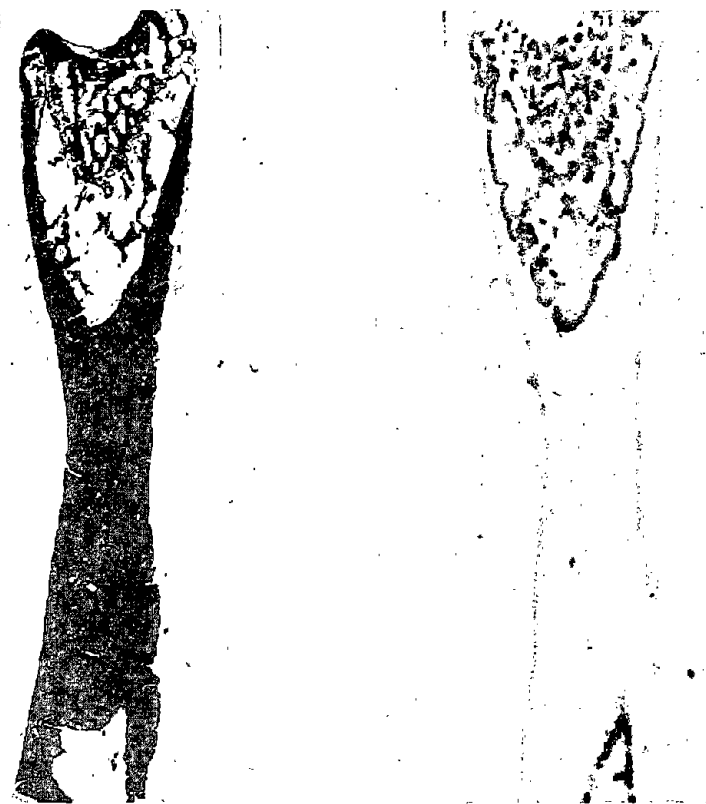


FIGURE 7.11. Similar to figure 7.10 but eight weeks after injection. (From Hamilton 1947. Reprinted with permission of Radiobiological Society of North America, Oak Brook, Illinois, copyright 1947.)

C. Metabolism of Plutonium in Man

The fact that thousands of MED workers would be handling plutonium, some of the conflicting information arising from the animal experiments, and the usual problem of applying data from animals to important quantitative figures needed for humans, generated a very strong desire to have direct information from man. Therefore, a program was begun in which selected hospital patients were given what were then regarded as tracer-level doses of soluble plutonium. Body excretions were collected. Since most of the patients were selected because they had a short life expectancy, some died moderately soon, and tissue samples were analyzed as were excreta. Others lived for many years, even long enough to cast doubt on the validity of the original medical opinion or to confirm the resiliency of the human organism.

Between April 1945 and July 1947, a total of eighteen patients received injections of soluble plutonium. Some were in "metabolism wards" of their respective hospitals where they were in-patients for disorders already requiring collection of excreta, measuring of food and fluid intake, etc. Three of them were at Billings Hospital of the University of Chicago, one was at the MED Hospital at Oak Ridge, eleven were at Strong Memorial Hospital of the University of Rochester, and three were at University Hospital at the University

of California, San Francisco. Those at Rochester and Chicago were in metabolism wards, the others in no special facility.

The first report came from California (Crowley et al. 1946) and was undoubtedly a stimulus to do further work since the metabolism in humans appeared to be rather different from what had been seen in the rat. While prolonged retention and selective deposition in the skeleton were common to both species, the elimination was at a higher rate in the rat to the tune of 50% of the administered dose against 5% for humans in an unstated period. Also, elimination in the rat was primarily via the feces, whereas the major elimination in humans seemed to be via the urine.

The first cases contributing the data on man were either the ones designated Cal-1 and Cal-2^(a) injected on May 14, 1945, and April 26, 1946, respectively, or Ca1-1 and Chi-1. Since the cited report by Crowley et al. is dated May 31, 1946, it is doubtful if Cal-2 could have contributed very much information. Besides, this was a very ill, four-year-old child with bone cancer. But an important conference held in May 1945 mentions two cases. Since there was one done at Chicago in April 1945, it is possible that they considered these two adults—one from California and one from Chicago.

The cases done at Rochester, designated HP-1 through HP-11, were strictly a cooperative operation between the Los Alamos Scientific Laboratory and the Rochester Project. Wright Langham came to Rochester to supervise the handling of the plutonium and general planning. Most of the radiochemical analyses were done at Los Alamos. It is not clear by what means the samples traveled from Rochester to Los Alamos, and they were plentiful as anyone who has ever been associated with such work knows well. In view of the security surrounding all plutonium operations, they may have been escorted, probably by Dr. Langham himself on a train. Rochester contributed the medical team of the Metabolism Ward and scientific collaboration from members of the MED project. The report, which is now a classic, was not issued until 1950. The authors were Wright Langham, Samuel Bassett, Payne S. Harris, and Robert E. Carter (1950), and acknowledgments were made to fifteen staff members of the two institutions. The report also states that Stafford L. Warren, medical director of the MED, was primarily responsible for initiation of the work. While the report was issued as a joint report of Los Alamos and Rochester, it bore a Los Alamos report number, and there was not much overt attempt to identify the institutional connections of the many workers. Thus, it remained somewhat mysterious except to those who had direct connection with it. This was aided by keeping it classified "Secret" for many years, then "Restricted," then "Official Use Only" since some of the patients were still alive, and at long last "unclassified." The latter action came in time to allow this report, carrying as it does many of the graphs and interpretations used for years in bioassay work on plutonium, to be included as a "landmark paper" in the special silver anniversary issue of the journal *Health Physics* in 1980. The authors include results not only from the HP patients but Cal-1, Chi-1, and Chi-2, and urinary plutonium assays from a few Los Alamos workers. The cases Chi-1 and Chi-2 were described also by Russell and Nickson (1946).

(a) It was the mountains of dirty glassware from Cal patients that started Patricia Durbin, then Patricia Wallace, in the position of "diener" at the Crocker Laboratory. Now we are indebted to her, among other things, for a complete and sophisticated review of all the human injection cases (Durbin 1971, 1972). Included for the first time is full information on Cal-2 and Cal-3.

A summary of the designation, date of injection, and other pertinent information for all eighteen patients is given in table 7.1, modified from an Energy Research and Development Agency (ERDA) press release dated February 1976.

TABLE 7.1. Summary Of Plutonium Injection Patients

Case	Age	Patient Data		Diagnosis	Injection	
		Sex	Race		Date	Place
Cal-1	58	M	W	Stomach Cancer (misdiagnosis)	5/14/45	California
Cal-2	4	M	W	Bone Cancer	4/26/46	California
Cal-3	36	M	B	Bone Cancer	7/18/47	California
Chi-1	68	M	W	Cancer of Mouth	4/26/45	Chicago
Chi-2	55	F	W	Breast Cancer	12/27/45	Chicago
Chi-3	Young adult	M	W	Hodgkins Disease	12/27/45	Chicago
HP-1	67	M	W	Duodenal Ulcer	10/16/45	Rochester
HP-2	49	M	W	Hemophilia, Heart Disease	10/23/45	Rochester
HP-3	49	F	W	Hepatitis, Hypoproteinemia	11/27/45	Rochester
HP-4	18	F	W	Cushing's Syndrome	11/27/45	Rochester
HP-5	56	M	W	A. L. Sclerosis	11/30/45	Rochester
HP-6	45	M	W	Addison's Disease	2/01/46	Rochester
HP-7	59	F	W	Rheumatic Heart Disease	2/08/46	Rochester
HP-8	41	F	W	Scleroderma	3/09/46	Rochester
HP-9	66	M	W	Dermatomyositis	4/03/46	Rochester
HP-10	52	M	B	Rheumatic Heart Disease	7/16/46	Rochester
HP-11	68	M	W	Cirrhosis of Liver	2/20/46	Rochester
HP-12	53	M	B	Severe Auto Accident Injuries	4/10/45	Oak Ridge

Source: Modified from an ERDA press release, February 1976.

Excretion measurements were obtained in the initial work as follows:

HP-1	24 days	HP-9	35 days
HP-2	27 days	HP-10	30 days
HP-3	23 days	HP-12	38 days plus 43 to 46 days
HP-4	23 days plus 79 to 82 days	Chi-1	to 138 days with a few breaks
HP-5	22 days	Chi-2	to 138 days with several breaks
HP-6	22 days	Chi-3	16 days
HP-7	28 days plus 79 to 85 days	Cal-1	to 138 days.
HP-8	64 days		

In addition, HP-6 provided four consecutive daily urine samples beginning at day 523 and another set beginning at day 1,610. HP-3 contributed four samples beginning on day 1,645.

Blood contents were measured in all twelve HP patients. Tissue samples were obtained and analyzed from HP-5, HP-9, HP-11, Chi-1, Chi-2, and Cal-1. A few samples were obtained also from HP-12.

The composite results of this rather large effort left no doubt that the experiment was essential to proper use of metabolism data to establish protection procedures for workers—and indeed for the general population. Even though the tissue samples were small, and the patients quite ill before their deaths, conclusions could be drawn:

1. There were no *major* differences in tissue contents between humans and the common laboratory animals with the exception of liver.
2. The amount in the liver of humans may be 20% to 40% versus 10% or less for rats receiving the same Pu +4 citrate complex.
3. The retention half-time in liver is greater in humans.
4. The retention half-time for total body in humans is estimated at 118 yr (range 84 to 175), much longer than in laboratory animals.
5. The excretion pattern is clearly different, as will be discussed below.

The urinary and fecal excretion for the 138 days of collections on the patients in this study is shown in figure 7.12. Also shown are mathematical expressions derived by the authors depicting the excretion as a power function of time. Note that in the early times fecal excretion exceeded urinary, as in the animals,

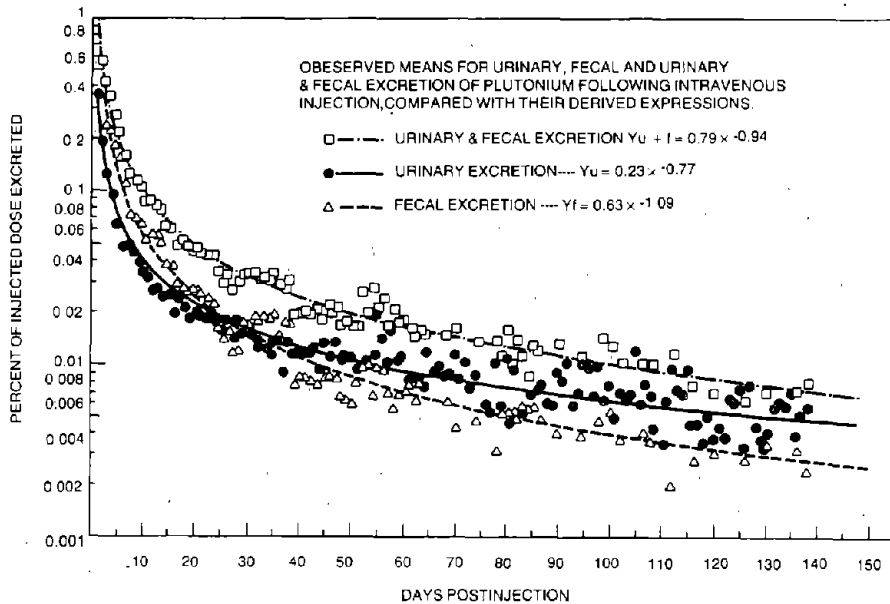


FIGURE 7.12. Excretion of plutonium by patients described in the text. The Y axis represents a rate % of injected dose excreted per day. In the derived expressions, Y = percentage of injected dose excreted each day, X = the time postinjection, and the subscripts refer to urine (u), feces (f) and urine and feces (u+f). (Redrawn from Langham et al. 1950.)

but after about 30 days the urinary component was the larger, quite different from the rat. (These were intravenous injections. Hence, the elimination of unabsorbed plutonium in the feces in the early period is not a complication as it would be for oral or inhalation exposures.) The original paper gives the complete data on each subject, the derivation of the expressions given, and much additional information.

The needs of a substantial bioassay program built on excretion measurements could not be met with data up to only 138 days. Therefore, Langham introduced an extrapolation based on excretion by workers at Los Alamos. Here the amounts were very small, and there was no independent measure of the amount of plutonium in the body. Thus, there is greater uncertainty than in the period up to 138 days. However, something was known about the exposures from the monitoring procedures. By translating a chronic variable exposure dose into an effective single dose between the limits of exposure at some effective time, some additional points could be added. An adjusted excretion expression was thus obtained:

$$Y_{ua} = 0.20X^{-0.74}$$

where Y_{ua} = adjusted urinary excretion rate and X is time. To do this, they assumed the excretion beyond 138 days was exponential to time and made estimates of an absolute minimum value for biological half-time.

The results, carried to 1,750 days, i.e., about five years, are shown in figure 7.13. Integration of this expression shows that even through 1,750 days urinary excretion accounted for only 6.3% of the total injected dose.

The demands of an assay program based upon such a small fractional excretion rate per day are obviously very great. Yet, these data and these curves formed the basis for practice in the MED and later in the AEC, although some modifications were introduced. The equation has been known as the Langham equation. While these graphs appeared in many postwar summary publications, they were without the details of derivation. It is primarily in the report LA-1151 that the whole story is shown. Since the paper has now at long last reached the open literature in the special issue of *Health Physics* (1980), its perusal by all interested is heartily recommended. There will be further discussion in chapter 16, including the results of re-examination in the light of postwar work. But, for the present, the work stands as a monument to what the MED people could do with less than ideal material to work with.

Comment: The fortuitous circumstance that four of the patients, three at Rochester and one in California, were still living in 1976, more than twenty years after injection, and that HP-1 lived fourteen years to age eighty-two, none of them showing any gross effects of the plutonium injection, lends credence to the view that the injections produced no measurable harm. Obviously, the group is so small that no statistical validity can be attached to this statement, nor can it be assumed that had the whole group lived more than twenty years no untoward effects would have been seen. Yet, these facts raise questions about the now popular slogan that "plutonium is the most toxic element known to man." We will return to this in a following section.

In chapter 2, we commented on the importance of the planned administration of uranium in man. The importance of the information gained from the planned administration of plutonium is at least an order of magnitude greater. Protection of all the workers in the Plutonium Project would have been immeasurably poorer without it. Yet, it is now clear that informed consent was

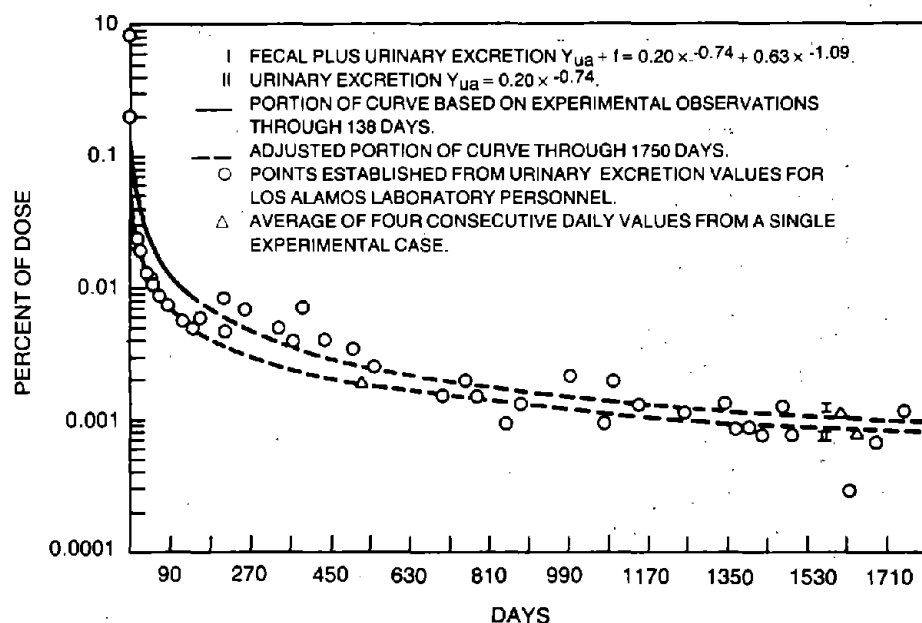


FIGURE 7.13. Excretion of plutonium over an approximately five-year period using the data from the patients described in the text and rates determined from Los Alamos workers to extend the time beyond that shown in figure 7.12. The derived expressions use the same symbols as in figure 7.12. (Redrawn from Langham et al. 1950.)

honored more in the breach than in the performance. (There was only one case of documented informed consent.) When it became obvious that public scrutiny could no longer be prevented by keeping a security classification around the work, there was something of an uproar in the Washington offices that had inherited the problem from MED and in turn AEC, i.e., ERDA; and covert apprehension in the university hospitals involved. After great travail, it was decided that those patients who were still alive should be informed of what they received.

Like many crises agonized over in the anticipation, the response was remarkably mild. (One patient was not informed because her doctor judged that the knowledge would be detrimental to her health.) Perhaps this was because the patients were so elderly that they felt they had already weathered hazards of much greater magnitude. But obviously in view of the reputation that plutonium has now, such an experiment would be unthinkable, with or without informed consent. Thus, we will have to be content with what could be gathered during the war years, plus extensions through workers in the postwar years, and eventually results from the U.S. Transuranium Registry (chapter 16).

Reiteration and reinterpretations of this work were obviously necessary as correlative information accrued during the postwar decades. These will be examined in succeeding chapters, especially the work of Durbin. But, for completeness, let us give the status of the patients as of 1976, close to the end of the years of factual review for this book.

Case	Status	Age at Death	Survival Time ^(a)
Cal-1	Deceased	79	20 yr 8 mo
Cal-2	Deceased	5	8 mo
Cal-3	Still living		
Chi-1	Deceased	68	5 mo
Chi-2	Deceased	55	17 day
Chi-3	Lost to follow-up		
HP-1	Deceased	82	14 yr
HP-2	Deceased	51	2.5 yr
HP-3	Still living		
HP-4	Deceased	20	2 yr
HP-5	Deceased	57	5 mo
HP-6	Still living		
HP-7	Deceased	60	8 mo
HP-8	Still living		
HP-9	Deceased	66	1 yr
HP-10	Lost to follow-up		
HP-11	Deceased	68	6 day
HP-12	Deceased	60	7 yr

(a) This is the time after injection, but death was always from causes unrelated to the presence of plutonium.

IV. Toxicology of Plutonium

Work on the biological effects of plutonium in animals was concentrated during the years of World War II at Chicago and Rochester. Berkeley remained more concerned with metabolism.

A. Acute Effects

The first description of the acute biological effects of plutonium, in contrast to inferences of effects from its metabolic behavior, is found in the report on the effects of "product" on a dog (Cole and Prosser 1945). This was a broad-gauge study in which most of the usual physiopathology used in clinical medicine was applied. The dose was large (0.36 mg/kg), and the animal's clinical condition went downhill so fast that it was sacrificed after sixteen days and four hours. Blood samples taken in the interim demonstrated a gradual drop in plasma protein, rather striking shifts in electrophoretic patterns (increase in α_2 globulin), and changes in blood chemistry similar to acute x-ray exposures (300 to 600 roentgen units) with some differences. The dog exposed to plutonium showed less hemorrhage than did dogs exposed to x rays, and ulcers of the duodenum and jejunum did not appear as they did after x-irradiation. The hematological changes were not remarkable in this short period except for a drop in the number of leucocytes in peripheral blood and some fall in erythrocyte count. Yet, the animal was obviously acutely ill; and insofar as one experiment has meaning, it demonstrated greater sensitivity to plutonium in the dog than in mice.

1. Effects in Rodents

Although there were other "notes" in Met Lab monthly reports, the next full report on effects appeared in the large report on *Toxicity and Metabolism of Plutonium in Laboratory Animals* written in August 1947 (R. D. Finkle et al. 1947). In chapter IV of the report, Snyder, Kisielewski, and Finkle describe the survival and growth of plutonium-injected animals; in chapter V, the effects of ingested plutonium (Snyder, Lawrence, and Finkle), and in chapter VI, the hematological effects (Jacobson and Simmons). Since this rather complete document did not get published, some details will be given here. The animals were mice (ABC and CF1), rats, and rabbits.

a. Lethal Action

The LD₅₀ in 30 days after intravenous injection in rats was about 0.09 $\mu\text{Ci/g}$, in 60 days 0.06 $\mu\text{Ci/g}$, at 90 days 0.06 $\mu\text{Ci/g}$, and at 220 days about 0.03 $\mu\text{Ci/g}$. The corresponding values for mice were 0.08 $\mu\text{Ci/g}$, 0.07 $\mu\text{Ci/g}$, and 0.05 $\mu\text{Ci/g}$ for 30-, 90-, and 210-day LD₅₀ values. These figures can be compared with those for fission products such as ⁸⁹Sr-⁹⁰Sr discussed in chapter 6. The LD₅₀ values for these are on the order of 5 to 8 $\mu\text{Ci/g}$. Thus, plutonium appears to be more toxic acutely by a factor of about one hundred. Allowing a factor of ten for the then-accepted relative biological effectiveness (RBE) of alpha particles, another factor of ten is left that requires some other explanation. If the currently advocated RBE of twenty for alpha particles is used, only a factor of five requires other explanation.

The data are presented in extenso in the original document.

b. Effects on Growth

Retardation of growth was detected at levels as low as 0.0078 $\mu\text{Ci/g}$ in rats and 0.0013 $\mu\text{Ci/g}$ in rabbits. This retardation began only after several weeks of apparently normal weight gain and a long plateau.

c. Clinical Findings

The rats showed extensive gastrointestinal hemorrhage, hyperemia of lymph nodes and gonads, and extensive liver damage. Skeletal lesions (fractures) were slower to develop and appeared at doses of 0.031 and 0.016 $\mu\text{Ci/g}$ in rats. One osteogenic tumor was seen and three soft tissue tumors, all after 150 days.

Symptoms in the mouse were comparable and in the same dosage region.

d. Mechanisms

The authors speculate that some of the toxicity seen may be due to *chemical toxicity* of plutonium as a heavy metal. This was stimulated in part by a shock-like syndrome occurring in the mice receiving intravenous doses as high as 200 mg. (A similar experience was encountered in rats receiving large intravenous doses of radium in the work at Rochester as mentioned in chapter 1.)

The idea of a specific chemical effect was strengthened further by the fact that the acute effects of plutonium proved to be about the same as those of similar quantities of ²²⁶Ra. Since at that time the simple calculation of relative energy and half-life of ²³⁹Pu versus ²²⁶Ra predicted that plutonium should be about one-fiftieth as radiotoxic as radium, the extra toxicity was concluded to be attributable to a chemical action. Other more probable explanations emerged later, but the idea of a component of chemical toxicity for plutonium reappears like a Phoenix throughout the literature, even to the present. Pathology was entirely consistent with radiation effects, however.

e. Effects of Ingested Plutonium

The number of animals was very small, and the almost negligible absorption from the gastrointestinal tract made this more a metabolism than an effects experiment. A dose of about 17 $\mu\text{Ci/g}$ was not lethal to the mouse but caused marked growth retardation as well as lethargy, labored breathing, etc., which cleared up by the forty-eighth hour.

f. Hematological Changes

At these acute levels, changes in hematological constituents of peripheral blood of the rodents were a very sensitive indicator of damage. The data in this report are, however, not complete, since many of the animals were still living at the time the report was written. On the whole, the experiment shows effects identical to those occurring with other radioactive materials, and there are not marked species differences. Also, the differences between external radiation with x rays, fast neutrons, and gamma rays and those of plutonium are qualitatively small. Unfortunately, it is not feasible to gauge from these data to what extent quantitative differences exist. The doses given were well below the LD_{50} levels for plutonium, and there seemed to be a threshold between 0.003 and 0.0003 $\mu\text{Ci/g}$ in mouse, rat, and rabbit. The numbers of animals were acceptably large, and the observation period was approximately three hundred days.

2. Effects in the Dog

An extensive clinical study of acute and subacute effects in the dog is presented by Painter et al. in an AEC declassified report (Painter et al. 1946). The report is about equally divided between careful and extensive studies of the metabolic behavior of plutonium and broad-ranging clinical physiology and physiopathology. Since this is another paper that was not published as planned in the NNES series, it will be examined in some detail. Fortunately, some of the findings are included in a paper by Prosser and collaborators in the Plutonium Project issue of *Radiology* in 1947. This provides many comparisons between external radiation and radioisotopes and among radioisotopes (Prosser et al. 1947; Prosser and Swift 1949).

The plutonium was used in its soluble +6 citrate form in all but one dog and was given by intravenous or intramuscular injection. Five dogs received high doses, eleven dogs "chronic low doses" but not low enough to be regarded as "chronic" today. There were four dogs and one puppy in the intramuscular series that received relatively lower doses.

a. Acute Toxicity

Although the series is small, the acute LD_{50} (death in about 15 days) was calculated. It was about 0.3 $\mu\text{g/g}$ (0.02 $\mu\text{Ci/g}$) net retained dose for intravenous administration and between 0.35 and 0.68 $\mu\text{g/g}$ (0.02 to 0.04 $\mu\text{Ci/g}$) for intramuscular injection. The authors consider this of the same order of magnitude as in the rat. Since the figures with the rat were more than double and were for 30 days it seems more correct to conclude that the dog shows greater sensitivity to plutonium acutely, despite the small size of the group studied. The "subacute" dose, with which the animals (adult mongrels) lived from 90 to 234 days, was less than a factor of two below the levels mentioned above. Either the dog is exquisitely sensitive to small differences in the size of a plutonium dose, or this pioneering series was too small to permit a valid quantitative measurement of toxicity.

b. Clinical Findings

This portion of the report gives a meticulous description of the clinical course of each dog with some exceptions.

Gross changes in appearance and activity of most of the treated dogs did not appear until a week or so before death. The general picture was comparable to x-irradiation, except there were fewer hemorrhages in the plutonium-treated animals. Fever and evidence of acute illness began about the tenth day but not in all cases; changes in heart rate were comparable to x-irradiated animals, but in this, like most other signs, the plutonium dogs seemed to be more variable. Hematological changes are presented in detail and are consistent with radiation effects. Body weight loss began almost immediately in the acute-level animals. At autopsy, the dog injected with plutonium that died acutely resembled "dogs which died two weeks after single doses of x-radiation except that hemorrhages and ulcers were less abundant." The x-ray dose producing comparable changes in a comparable time was 50 r per day.

The picture was quite different between the two subacute dogs. One died at 90 days and resembled dogs who had received "several months of treatment with 12.5 r daily x-radiation" in that anemia was an important factor. The other dog, which lived 234 days, showed marked liver damage much like that seen in rodents. There was no leukopenia or anemia. Since the dogs were mongrels, this difference may represent lack of comparable genetic make-up, but no proof can be offered. The case does speak well for the movement that began about this time to employ only genetically homogeneous animals in such important and expensive work.

3. Summary of Clinical Findings in All Animals

In the plutonium conference held in May, 1945 (Nickson 1945), Brues summarized clinical effects of plutonium. A few items are in addition to those in the CH-3783 report and a few differ. At acute levels:

1. CF1 mice show only slight anemia, while ABC mice show profound anemia at the same dose.
2. Gross renal damage occasionally follows lethal doses of plutonium.
3. The acute lethal dose is quoted as 0.4 mg/kg in the dog and 1 mg/kg in rodents given intravenous doses, while it is 4.5 mg/kg in mice after intramuscular injection. These are roughly comparable to the figures discussed earlier.
4. Subacute plutonism is described in which the animal survives for many months although declining gradually (e.g., 0.3 mg/kg of +6 citrate).
5. Some hematological effects occur in some groups of animals at all doses down to 0.05 mg/kg, while in others the first significant changes occur at 0.1 to 0.25 mg/kg.
6. Amounts as small as 1 μ g deposited locally may produce ulceration and suspicion of carcinogenic changes.

Throughout this summary, the great variability of response between one group of animals and another is emphasized. No explanations were forthcoming at the time.

At this same conference, the first formal comparison was made of the toxicities of radium and plutonium and of polonium and plutonium. This was reported by R. M. Fink and is the first introduction of work at the University of Rochester. This will be reviewed in the section on chronic toxicity.

4. Summary of Histopathology

The microscopic pathology after acute doses of plutonium was not dwelled upon voluminously during the work of the war years. This was due in part to the similarity to x-irradiation and partly to the much greater interest in examining the longer-term effects. Yet, there was the usual thorough study done by Bloom. In his remarkable treatise on the histopathology of radiation (Bloom 1948), of about one hundred mice used a large number were examined within a few days of injection, while the longest period given is seven months; ditto for the thirty-four rats receiving plutonium. The results are given organ by organ, system by system, and in relation to external radiation and other radioisotopes. No isolated summary can be given except to remark that the plutonium effects tended to be "focalized." In a summary paper in *Radiology* (1947), Bloom stresses the marked difference experienced between rats and mice vis-à-vis bone-seeking elements. In mice, "since we see the mice when they have practically ceased growing, the experiments with the radioactive isotopes in these animals would correspond fairly well to the deposition of these substances in adult human beings. In the case of rats, the effect of bone-seeking isotopes is a bit different, since the rat is, for all practical purposes a continuously growing animal. In the rat the isotopes that seek bone come down not only in old bone but predominantly in the zone of new bone growth in the metaphysis, and for all practical purposes they kill this entire zone" (Bloom 1947, pp 346-347). Examples are given.

In the 1945 plutonium conference cited earlier (Nickson 1945), the Chicago group introduced estimates concerning the relative histopathology of x ray, ^{89}Sr , plutonium, and radium. By the use of a numbering system for degree of damage, a procedure that most pathologists seem to shun like a plague, they presented some interesting correlations. They are reproduced here as table 7.2. It is unusual, and may be regarded as an example of the simpler days when broad correlations of new information were more important than minutiae of specific problems.

5. Effects on Tissue Metabolism

An almost unique contribution to studies on the effects of radioisotopes is the work of Barron et al. (1946) on the tissue metabolism of rats treated with plutonium. In the chapter on uranium (chapter 2), we reviewed work showing the effect of uranium on the metabolism of isolated cells. The plutonium work was entirely different in that the studies were made on tissues removed from animals after the development of acute plutonism.

They found both respiration without substrate, and oxidation of pyruvate and anaerobic glycolysis were greatly depressed in spleen tissue from the affected animals. Liver showed similar decreases in metabolic rates, and these seemed to be correlated with the degree of macroscopic atrophy seen. Phospholipid synthesis was not affected.

Using ^{32}P as a tracer, they found that its transport across the intestinal wall was not affected.

Metabolism of the adrenals was profoundly affected, while kidney showed some but lesser changes. Heart, submaxillary gland and lungs (after intratracheal instillation) were essentially normal. After ingestion of plutonium, there was inhibition of oxidative processes in small intestine, but anaerobic glycolysis remained normal.

TABLE 7.2. Comparison of Histological Effects of X-Ray (single dose), Radium, Plutonium, and Radiostrontium*

Agent	Dose	Range of Intervals	Bone Marrow-rbc	Bone Marrow Gran.	Bone Marrow Growth Damage	Cut Epithelium	Gut Lymphatic	Mes. Lymph Node	Skin	Spleen Lymphatic Damage	Spleen Myelopoiesis Damage	Spleen Myelopoiesis Stim	Testis	Ovary	Thymus	Liver	Other Organs
X-ray	350 r	1hr-21d	10a	8n	0	4n	3n	3n	0	2n	8n	6n	0	2e	4n	0	0
Sr ⁹⁰ IP	1.0 μ C/g	1d-5mo.	10b	9b	2e	0	—	0	—	0	0	4n	—	—	—	—	—
Plutonium IV	1.25 μ g/g	6hr-42d	6e	6e	4e	0	2a	2a	—	+e	6b	6e	6e	?	+e	+e	0
Plutonium IM	4.5 μ g/g	4d-14d	4d	6e	4e	0	+e	+e	—	+e	0	4e	0	—	0	0	0
Plutonium IM	1.5 μ g/g	1d-60d	5d	6e	4e	0	+e	+e	—	+e	0	6e	6e	—	0	0	0
Radium IP	1.0 μ g/g	3hr-40d	10e	9e	8e	±	6e	6e	—	6e	0	2e	9e	—	+e	0	0

* The numbers 1-10 refer to degree of damage from 10% to virtually 100% destruction. All are very rough estimates. The letters "a-e" refer to the extent of recovery from the height of damage, 80% to 10%. The letter "n" indicates complete recovery. Under "Spleen Myelopoiesis - stimulation" the figures are relative only and do not indicate multiples of the normal. The letters under this heading indicate return to normal as in the regeneration from damage. Other signs have the following meaning:

+ damage incapable of quantitation
 ? insufficient data
 0 no change
 ± questionable change
 — not examined

Source: Reset from Nickson 1945.

Studies such as this are very difficult to interpret. With considerable atrophy of some tissues or organs, the weight of live tissue contributing to the metabolic processes is difficult to gauge. Without a measure of this quantity, changes in metabolic rate per gram of sample may be quite misleading. Also, it is difficult to separate out effects of plutonium per se and secondary effects due to the general illness produced by the plutonium. While popular for a while in toxicology, work of this type did not continue much longer because effects on specific enzymatic processes could contribute more information.

Thus, while this study is unique, it is of interest primarily to show what was thought and what was tried rather than for its contribution to the understanding of plutonium toxicology.

6. Recap of Acute Toxicity: Comparison to Radium

In the later years of World War II, the results of two major animal experiments began to yield useful information. These were the studies at the University of

Rochester Project (chapters by Boyd et al. [1950a,b] in Fink 1950) reported in some detail in chapter 1 and the early results of a series of experiments at Chicago. Although the reports are post-World War II, the work was done either entirely (Rochester) or in the acute phases (Chicago) during the war years and should be considered in this chapter devoted to that period.

As soon as it was known that plutonium was a bone seeker and was retained avidly in the body, analogies to radium were drawn, as we have already seen. The quantitative aspects as they bore on standard-setting will be looked at in detail in chapter 16. Suffice it to say here that the early investigators were clairvoyant enough to let the differences in microdistribution in bone of these two elements raise a red flag to basing conclusions on simple calculations of relative energies and half-lives.

The first information on acute toxicity seemed to confirm the wisdom of this cautious approach. But conclusions had to wait for some quantitatively reliable data with plutonium and radium compared in the same experiment. We will consider the acute toxicity in this section.

The toxicity of ^{239}Pu relative to ^{226}Ra in the Rochester rats is given in table 7.3, modified from Boyd et al. 1950a, p. 251. Obviously, ^{239}Pu is markedly more effective than ^{226}Ra as an acute toxic agent on a microcurie basis.^(a) Part of the phenomenon lies in the surprisingly low toxicity of ^{226}Ra acutely.

TABLE 7.3. Toxicity of ^{239}Pu Relative to ^{226}Ra

Days Following Injection	Approx. LD ₅₀ ($\mu\text{Ci/kg}$)		Pu/Ra Toxicity Ratio
	Ra	Pu	
10	8000	200	40
20	4000	130	30
30	3000	100	30
60	1300	60	20

Source: Modified from Boyd et al. 1950a.

An analysis by Brues (1951) contains not only the Rochester and Chicago data but a 1914 experiment (Proescher and Almquest 1914). The results are shown in table 7.4, modified from Brues (1951).^(b)

The toxicity of plutonium relative to radium is about thirty at thirty days in both studies. But note that the ratio seems to be decreasing with the time span in table 7.3. This is important, as we will see soon.

All of this work refers to acute lethality, not the development of any specific pathologic entity. It solidifies the view expressed earlier that plutonium is considerably more toxic than radium, rather than a factor of fifty less, as the relative half-life and energy deposition would predict (see chapter 16). We have already noted that plutonium is more toxic acutely than the fission products by a factor of one hundred. Those who had urged extreme caution in handling plutonium were very glad they had insisted on their position, despite the extra costs in

(a) On a weight basis they are nearly equal.

(b) Note that the units are microcuries per kilogram in table 7.3 and microcuries per gram in table 7.4.

TABLE 7.4. Estimates of the Thirty-Day LD₅₀ for Intravenously Injected ²²⁶Ra and ²³⁹Pu

Species	Approx. 30-day LD ₅₀ (μ Ci/g)	Source
— Radium-226 —		
Rat	1.3	Proescher and Almquest (1914)
Mouse	<2.0	Proescher and Almquest (1914)
Rat	3.0(a)	Boyd et al., ch. 7 in Fink (1950)
Rat	1.4	Boyd et al., ch. 8 in Fink (1950)
Male mouse	1.1	Norris and Evans (1946)
Female mouse	<2.2	Norris and Evans (1946)
Rat	0.9(b)	Norris and Evans (1946)
— Plutonium-239 —		
Rat	0.10	Boyd et al., ch. 7 in Fink (1950)
Rat	0.07	Boyd et al., ch. 8 in Fink (1950)
Dog	0.028	Prosser and Swift (1949)
Mouse	0.069	Snyder et al. (1949)
Rat	0.075	Snyder et al. (1949)
Rat	0.06	Brues (this study)
Mouse	0.05	Brues (this study)

(a) Dependent on polonium content of radium injected.

(b) Average of two series.

Source: Modified from Brues 1951.

construction and operations within the MED (cf. Seaborg quotation earlier in this chapter).

Does this information prove that plutonium is “the most toxic element known to man”? Hardly, as we will see in a later section.

B. Long-Term Toxicity of Plutonium

1. Survival and Lethality

Major efforts were expended in the postwar years to address all aspects of the long-term toxicity of plutonium. For the moment, we will examine only the information gained during the war years and analyzed immediately thereafter.

The Rochester experiment was done and reported in two phases, as described in chapter 4. The “pilot studies” employed fewer animals per point, but the dosage range was greater than in the larger “simultaneous studies” (see also description in chapter 1). Figure 7.14 shows the survival time of the Rochester rats up to three hundred days as a function of injected dose of ²³⁹Pu, ²²⁶Ra, and ²¹⁰Po in microcuries per kilogram in the pilot experiment. Note that the relative toxicity of radium seems to be increasing rapidly with longer survival times and might even approach a ratio of 1:1 versus plutonium if sufficient time were involved. The same picture appears if the ordinate is expressed as calculated radiation dose. In figure 7.15, the same data are plotted on a weight basis. Here we see the near equivalence of radium and plutonium and the far greater effectiveness of ²¹⁰Po in producing lethality because of its high specific activity.

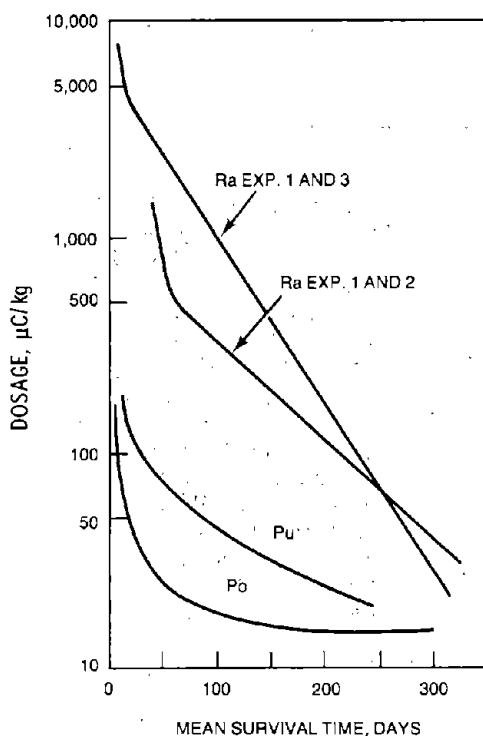
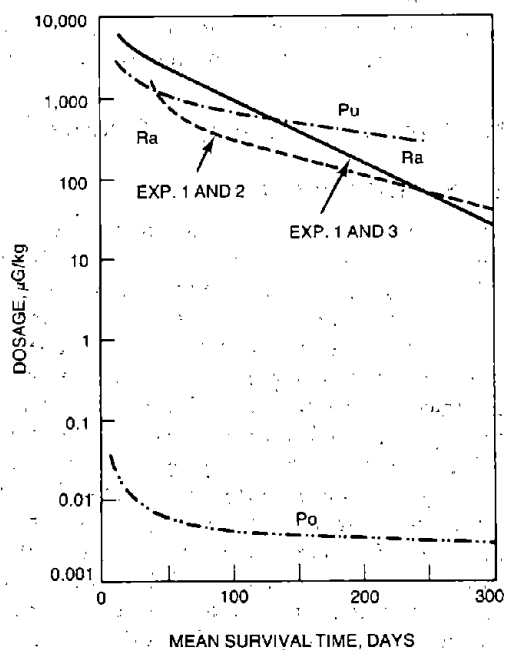


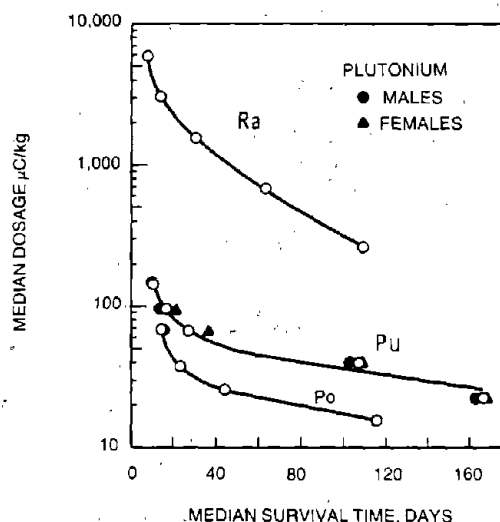
FIGURE 7.14. Mean survival time of Wistar-Rochester rats as a function of intravenously injected dose of ^{226}Ra , ^{239}Pu , or ^{210}Po . The radium experiments differed in their polonium content. Experiment 1 had 0.1 ^{210}Po , experiment 2 had 0.2, and experiment 3 had 0.07. This difference was due, of course, to waiting different times after the last purification of the radium preparation. Experiments 1 and 3, having the least polonium, are probably the best representation of ^{226}Ra . (Redrawn from Boyd et al. 1950a.)

FIGURE 7.15. The same experiments as plotted in figure 7.14 but on a weight basis. Note that plutonium and radium are almost identical on this basis. (Redrawn from Boyd et al. 1950a.)



In figure 7.16, the data from the simultaneous experiment are shown. Here there were many more animals per point, but unfortunately the choice of doses for radium did not extend much beyond 110 days survival time, and the whole experiment covers survival times only up to 160 days.

FIGURE 7.16. Comparative toxicity of ^{226}Ra , ^{239}Pu , and ^{210}Po in the much larger simultaneous intravenous experiment in the Rochester-Wistar rat. (Redrawn from Boyd et al. 1950b.)



Obviously, the same general trend appears toward a lower ratio of plutonium to radium with longer survival times. But no ratio for truly chronic periods can be decided upon. It can be concluded that the ratio of thirty seen for LD_{50} in thirty days is probably too high for application to longer periods. Indeed, the Rochester group calculated toxicity relative to radium, including some extrapolation from plotted curves as shown in table 7.5. Obviously, it cannot be said that the toxicity ratio becomes unity at longer times.

TABLE 7.5. Calculation of Plutonium/Radium Toxicity Ratio From the Rochester Experiments

Days After Injection	Approx. LD ₅₀ (μCi/kg)		Approx. Toxicity Ratio
— Pilot Experiment —			
	Ra	Pu	
100	600	40	15
200	150	23	6.5*
300	30	15	2.0**
— Final Data Compilation± —			
60	—	—	16
80	—	—	12
100	—	—	9

* This ratio was not calculated by the authors because of the small number of animals. It is done here for convenience more than significance.

** By extrapolation of the plutonium curve in figure 7.14.

\pm From the authors' final summary using their views on the validity of each set of data contributing.

Source: Modified slightly from Boyd et al., chapters 7 and 8 in Fink 1950.

To give the reader a better feel for the real data, since the previous figures show either no points or median values, figure 7.17 is reproduced from the Fink volume (p. 332). It shows the survival times of rats against the microcuries of plutonium injected per kilogram of body weight.

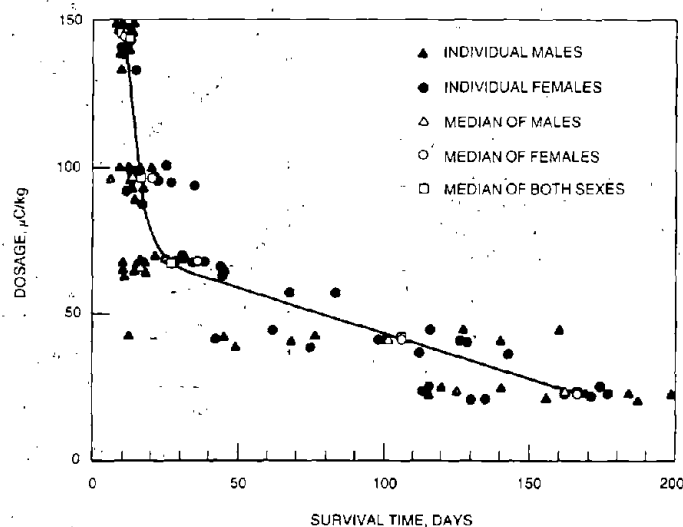


FIGURE 7.17. Survival curve of Rochester-Wistar rats versus microcuries of plutonium injected per kilogram body weight showing individual points and median points. (Redrawn from Boyd et al. 1950b.)

The issue of what the relative toxicity is at very low doses of plutonium or radium was addressed by Brues (1951) in the paper already discussed. He plotted curves for 5%, 10%, and 50% survival and obtained ratios of plutonium/radium of 12.8, 9.8, and 14.1, respectively. Here the ratio appears nearly invariant with dose rather than converging at lower doses. By calculating a survival function:

$$\alpha = \frac{1}{t} - \frac{1}{t_0}$$

where t is the survival time of the treated groups and t_0 that of the control group; and assuming each reciprocal of survival times represents a "rate of aging," they calculate also a survival function, β . This is defined as α/dosage and has been observed to be invariant over a wide range of doses of x-irradiation. Putting all of their findings with rodents, the Rochester data, and some figures for dogs and rabbits into the system, they calculate values of the function for each experiment. They ranged from 0.8 to 3.5×10^{-5} for radium and from 7 to 31×10^{-5} for plutonium. This would argue that the toxicity ratio is relatively invariant, or at least that it shows no regular trend with dose.

The Chicago workers conclude that the problems of too little information at low doses and long survival times in the Rochester data and problems of infectious pneumonitis in the animal colony at Chicago leave the final decision for further experiments. But they propose that the most probable ratio of toxicity of plutonium to radium in the intermediate dosage range is ten for long-term effects. This would be an underestimate for shorter-term effects.

This is how the situation stood at the end of the war work. All of it was based on survival times, not specific pathology. Brues went to the Tri-Partite Conference on Internal Dosimetry in 1949 (see chapter 16) with a figure of fifteen in his mind for long-term relative toxicity ratio. In chapter 8, we will see that the enormous surge of postwar work on plutonium toxicology supports the view that ^{239}Pu is at least ten times as effective as ^{226}Ra in producing many specific long-term pathological changes such as bone cancer.

2. Long-Term Pathologic Changes

The two large experiments at Rochester were not at low enough doses to see truly long-term pathologic changes. There is careful documentation in the chapters on both the "Pilot Studies" and "Simultaneous Studies" for the findings in animals dying up to 260 days after injection. Marked changes, comparable to doses of about 550 R of whole-body x-radiation, were produced in the hematopoietic system, bone, and testes. There were occasionally changes in lung, liver, stomach, kidney, heart, adrenal, and subcutaneous tissue. The primary effect was loss of functional cells and atrophy in the hematopoietic system and testes, mostly degenerative changes in bone and cartilage with disorganization of the areas of bone growth, and hemorrhages in numerous organs. These were not universal in occurrence except for the changes in bone. Liver showed mild to marked changes depending on dose.

The Rochester animals did not survive long enough, at least not in sufficient numbers, to show the development of bone cancer, and the pathology reports are essentially silent on the presence or absence of precancerous changes.

The first substantive discussion of carcinogenic changes came from Brues, Lisco, and M. Finkel (1946). Their findings with fission products have already been described (chapter 6). Bone tumors appeared in the rodents less frequently following administration of plutonium than after ^{89}Sr . They attribute this to the fact that many of the plutonium animals died from other causes (e.g., liver damage) before bone cancers could develop. They also postulate that the latent period for bone tumor development is considerably longer with plutonium than with strontium, although they give no information about the basis for this postulate. However, they did find what appeared to be osteogenic sarcomas. The date of preparation of this report is unknown; the year of declassification is 1946. Thus, the fact that plutonium could produce bone tumors as does radium must have been known within the MED biomedical community by at least 1945. The lowest dose inducing an osteogenic sarcoma within five hundred days in rodents was 0.02 mg/kg (1.25 $\mu\text{Ci/kg}$).

In a published summary of this work in the Radiology Symposium (Lisco, Finkel, and Brues 1947), it is stated that bone tumors were seen "frequently" in mice, rats, and rabbits at plutonium injection levels ranging from 0.05 to 4.5 $\mu\text{g/g}$, with a minimal latent period of two hundred days. The majority of the tumors occurred in the spine, in contrast to the sites of incidence with strontium (62% versus 22%). This difference was considered as possibly due to the greater affinity of plutonium for collagenous tissue than for bone mineral.

No liver tumors were reported in either the earlier or later work except for small adenomata. The authors remark on the severity of the effects in liver, which is ordinarily considered fairly radioresistant.

3. Is Plutonium the Most Toxic Element Known to Man?

This statement was made during the war years, perhaps in part to ensure support for the needed protection measures, in part to secure full cooperation of

the workers, and in part because the accumulating data were pointing in that direction. Like all such sweeping generalizations, it is a considerable exaggeration.

As we have seen in this chapter, plutonium (i.e., the isotopes of most concern for their biomedical effects, ^{238}Pu and ^{239}Pu) are far ahead of the fission products in acute toxicity. But in comparison to the "supertoxics" in the world of chemical toxicology, plutonium is far behind. This was discussed by Stannard (1976) in a summary paper, some data from which are excerpted in table 7.6, along with some of the data from this chapter.

TABLE 7.6: Acute Toxicity of Plutonium Compared to "Supertoxics"

Substance	LD ₅₀	Route	Test Organism
Botulinus toxin A	$5 \times 10^{-6} \mu\text{g/kg}$	IPR	Mouse
Crystalline botulinus toxin	$7 \times 10^{-9} \mu\text{g/kg}$	IPR	Mouse
Diphtheria toxin	$1 \times 10^{-4} \mu\text{g/kg}$	IPR	Mouse
Bufotoxin	$390 \mu\text{g/kg}$	IV	Cat
Curare	$500 \mu\text{g/kg}$	IPR	Mouse
Strychnine	$500 \mu\text{g/kg}$	IPR	Mouse
Potassium cyanide	0.3 mg/l	INH	Human*
Hydrogen cyanide	1.0 mg/kg	INH	Human*
Methyl mercury	7 mg/kg	Ingestion	Guinea pig
Arsenic trioxide	1000 mg/kg	Ingestion	Human
Plutonium	0.3 mg/kg	IV	Dog
	1.4 mg/kg	IV	Rat ^(a)
	1.3 mg/kg	IV	Mouse ^(a)

* Estimated from accident experiences and extrapolation from animal tests.

IPR = Intraperitoneal

INH = Inhalation

IV = Intravenous

(a) From this chapter, part IV A.

Source: Modified from Stannard 1976. Reprinted with permission of J. W. Press, Salt Lake City, Utah, copyright 1976.

There are indeed many substances extant that are far more dangerous in terms of acute exposure than is plutonium. There are even some radioisotopes of greater concern acutely, e.g., ^{210}Po and some of the transplutonic. However, they are not as available in quantity as plutonium might be.

What of long-term chronic toxicity? We have seen in this chapter that plutonium is well toward the head of the list in terms of effects on survival on an activity basis. But on a weight basis, it and radium are essentially equal. The wartime work stopped short of finding how effective plutonium really is as a carcinogen; this will unfold in chapter 8.

Meanwhile, perhaps we should, in anticipation, modify the statement to: "Plutonium is probably quite an effective carcinogenic agent in the bone of experimental animals." More will appear in chapter 8, including the fact that strontium can actually produce more tumors at its most effective dose levels.

V. Wartime Biomedical Work with the Transplutonic and Related Actinide Elements

A. General Considerations

By transplutonic elements we mean, of course, those with atomic numbers above plutonium. For our present purposes, these are primarily americium (element 95) and curium (element 96), but we will consider also neptunium and protactinium, which are below plutonium. The still heavier elements, although brought into being in part before the end of the war, did not receive biomedical research attention until later and will be omitted for the present.

Compared to plutonium and the fission products, these elements do not occur in large enough quantities to present the "new dimensions" described for plutonium. Yet, they have properties that make it important that they be reckoned with.

B. Metabolism

Figures 7.4 and 7.5 give the broad perspective on metabolism of these elements in bone and liver, which are the principal sites of deposition. All of them deposit in bone and remain for long periods, but the uptake is significantly less than for plutonium. Curium and americium, in which we are most interested, deposit to less than half the extent of plutonium. Neptunium deposits to almost the same extent as plutonium. On the other hand, americium and curium deposit to a much greater extent in liver than does plutonium. Very little neptunium deposits in liver. But those that deposit in high concentration also leave the liver very rapidly so that by sixty-four days all but neptunium are about equal in amount in liver.

Americium-241 was studied in some detail by the Berkeley group and reported on in the open literature by Scott et al. (1948b). This report expands on the facts noted above from the Hamilton review. The high content of liver initially and lower but more permanent fixation in bone are shown in table 7.7, modified from Scott et al. (1948b).

Obviously, the total amount in liver initially is impressive, but it is bone that holds essentially constant in content, while liver rapidly loses its americium. Incidentally, as the liver loses, the feces gain, which supports the notion that the americium is excreted in the bile.

These were complete balance experiments and included collection of excreta. Like plutonium in the rat, feces contained by far the larger fraction of total excretion, except in the first day. But it kept rising with time even to the end of the experiment.

Autoradiographs showed microdistribution in bone much like the rare earths and plutonium, i.e., deposition largely on the trabecular surfaces. In addition, americium seemed to accumulate around the small blood vessels of cortical bone. Cerium and element 61 (now promethium) were the only other radioelements

found to exhibit this particular deposition up to the time of this paper. Curium was added in the next year.

Of the other soft tissues, only kidney showed accumulation of significant amounts in the one- to sixteen-day interval.

Curium-242 was studied soon after americium also by the Berkeley group (Scott, Axelrod, and Hamilton 1949). At that time, it was the heaviest known element. The experiments and the results were closely similar to the work with ^{241}Am . The bone and liver contents are so much like those shown in table 7.7 that a separate presentation seems unnecessary. There was the same rapid loss from liver and build-up in feces, but the loss after 120 days was somewhat slower than for americium.

TABLE 7.7. Distribution of Americium-241 in Selected Tissues of the Rat after Intramuscular Injection

Time, days	Liver		Bone	
	%/Organ	%/g	%/Organ	%/g
1	54.8	6.07	23.2	1.01
4	35.7	4.24	19.1	0.66
16	15.3	1.64	25.6	1.25
64	1.94	0.18	25.0	0.96
256	0.68	0.081	24.8	0.94

Note: The data have been corrected for the fraction unabsorbed at site of injection and deviation of recovery values from 100%.

Source: Modified slightly from table II, Scott et al. 1948b. Reprinted with permission of American Society of Biological Chemists, Inc., Bethesda, Maryland; copyright 1948.

The microdistribution in bone seen by autoradiography was similar to that for americium, plutonium, et al. This included deposition around blood vessels in cortical bone.

The almost identical behavior of these two transplutonic actinides is consistent with the theory of the actinide series (see Scott, Axelrod, and Hamilton [1949] and Seaborg [1963] and other papers listed in the bibliography). Actually, much the same pattern is seen in the lanthanide rare earths since the chemical properties depend on the outer valence electrons, and these remain essentially the same. The additional electron for the successive elements goes into the 4f-electron shell, which is not complete. Among other things, the actinide series theory predicts very stable +3 valence states for members like americium and curium. This was found to be true and helped in their separation. Thus, on general principles we would predict that these would be poorly absorbed from the gut, as is plutonium. This is shown to be true for both elements in the papers cited.

It is tempting to argue for these elements, as was done for plutonium, that the high liver content reflects entrapment of colloidal aggregates by the RES. This is negated in both cases by the fact that spleen takes up only about one-fiftieth of the concentration in liver, even at early times.

Neptunium-237 has such a long half-life (2.2 million years) that it requires 1.5 mg to produce an activity of 1 μ Ci. Therefore, it seemed likely that chemical toxicity problems would predominate with it if there is to be any toxicological problem at all. This and other neptunium isotopes were studied to only a limited extent during the war. Very recent postwar work has cast it in a somewhat different light.

C. Reasons for Interest in the Transplutonium Elements

The inherent interest in checking biological and biochemical behavior of not only the transplutonium elements but all members of the lanthanide and actinide series is sufficient to stimulate biomedical investigations, especially on the "metabolism" of the various members as a function of their relative position in their respective series. But there are also some quite practical reasons for interest:

1. The transplutonics are formed by successive neutron capture reactions in nuclear reactors and in fission weapons. In the former, they may accumulate in sufficient quantity to require personnel protection and understanding of their behavior vis-à-vis plutonium.
2. Most of them are alpha emitters or decay by spontaneous fission, and all are radioactive. Their half-lives are shorter than that of ^{239}Pu , and they have high specific activities. The mass required to be biologically significant may be hardly measureable. Thus, they must be followed through their radioactive properties.
3. The relative biological effectiveness of elements that decay by spontaneous fission is quite high.
4. Americium-241 is a daughter product of ^{241}Pu , which may occur alongside ^{239}Pu in considerable quantities. It has utility for bioassay because of its 59.5-KeV gamma ray. But we must also reckon with it as a product of reactor operations and in weapons debris.
5. Toward the end of the war, the properties of some of the transplutonics for special uses as heat sources and in medical applications led to much interest in producing them in much larger quantities than even the normal accumulation in the production processes then extant. This stimulated even more interest in their biomedical behavior. The story will unfold in subsequent chapters.

VI. Summary and Commentary

The second major new dimension that faced the biomedical community with the decision to explore nuclear fission energy was a qualitative as well as a quantitative one. The synthesis of plutonium and the development of the radioelements of the actinide group posed virgin territory to explore. There was no previous experience to draw upon for predicting their metabolic behavior. Furthermore, the plans called for the production of kilograms, even tons, of some of these new elements that had to be produced in huge reactors and purified in enormous chemical separations plants.

The chemistry of the actinide elements is so intimately bound up with the biomedical studies that the chapter contains a summary of it. This includes the realization that the old periodic table of the elements was not correct in the

region of the new heavy elements and depiction of the modified periodic table as it was rewritten by the Seaborg group.

The early biomedical work on these new elements began at Berkeley, as it did with the fission products. Its genesis is outlined in the chapter. The basic behavior seemed much like radium, but, as with the fission products, autoradiography demonstrated some real differences in microdistributions. As the newer actinides were synthesized, the similarities and differences became even more apparent.

In addition to metabolic work, there were major studies on effects of plutonium at the Metallurgical Laboratory in Chicago and at the University of Rochester Project. There was also much activity in terms of monitoring of employees and determination of the kinetics of excretion at Los Alamos. The Chicago and Rochester work included both larger groups of animals and larger animals than did the Berkeley tracer studies. Though plutonium was obviously a bone seeker, there were sufficiently different microdistributions to raise warnings regarding any simplistic calculations of maximum allowable concentrations or body burdens. As the effects work progressed at both Chicago and Rochester, it became apparent that plutonium was considerably more effective than radium as a carcinogenic agent. This was puzzling since both were alpha emitters, and plutonium had both a lower energy and a longer half-life than radium. The explanation concerned the Chicago and Berkeley workers during most of the later war years and generated large experiments for further checking. These were done mostly in the postwar years. The cause turned out to be the difference in microdistribution.

There has been no large population of humans exposed to plutonium as there was to radium. There were occupational exposures, not only to plutonium, but to the other actinides, especially at Los Alamos. A number of hospital patients at California, Chicago, Oak Ridge, and Rochester received tracer quantities of plutonium and were studied as long as possible. Basic metabolic behavior appeared to be similar to that seen in the animal experiments and supported the then-extant exposure limits.

Right at the end of the war, in 1947, the data for plutonium and the other actinides were used at a series of three-nation conferences on radiation exposure limits (The Tri-Partite Conferences). They required careful interpretation, for the most conservative interpretation could have closed Los Alamos. Details are reserved for chapter 16 on standards.

During the war years, a good start was made on the inhalation toxicology of plutonium. This involved primarily Richard Abrams at Chicago. Details are reserved for chapter 9.

Whereas the wartime investigations of the fission products went far toward answering the major questions, the work with the actinides seemed to keep opening almost as many questions as it settled. Therefore, there was a large carry-over into the postwar years, as described in chapter 8.

References

- Allison, S. K. 1944. *Metallurgical Laboratory monthly progress report for February 1944*. MUC-NH-807.
- Barron, E. S. G., R. Abrams, R. D. Finkle, and R. P. Rhoades. 1946. *The effect of plutonium on tissue metabolism of rats*. Metallurgical Laboratory report CH-3849, AEC report MDDC-1653.

- Bloom, W. 1947. Histological changes following radiation exposures. *Radiology* 49: 344-48.
- Bloom, W. 1948. *Histopathology of irradiation from external and internal sources*. National Nuclear Energy Series, div. IV, vol. 221. New York: McGraw-Hill.
- Boyd, G. A., H. E. Silberstein, R. M. Fink, A. Frenkel, W. L. Minto, R. G. Metcalf, G. Casarett, and G. M. Suter. 1950a. Pilot studies on the intravenous lethal dosage of polonium, plutonium, and radium in rats. Chapter 7 in Fink 1950, pp. 211-94.
- Boyd, G. A., A. Williams, W. L. Minto, D. V. Tiedeman, R. M. Fink, G. Casarett, and R. G. Metcalf. 1950b. Simultaneous studies on the intravenous lethal dosage of polonium, plutonium, and radium in rats. Chapter 8 in Fink 1950, pp. 295-404.
- Brues, A. M. 1951. *Comparative chronic toxicities of radium and plutonium*, ANL-4625. Argonne, Ill.: Argonne National Laboratory.
- Brues, A. M., H. Lisco, and M. Finkel. 1946. *Carcinogenic action of some substances which may be a problem in certain future industries*. AEC report MDDC-145, declassified July 31, 1946.
- Carritt, J., R. Fryxell, J. Kleinschmidt, R. Kleinschmidt, W. Langham, A. San Pietro, R. Schaffer, and B. Schnap. 1947. The distribution and excretion of plutonium administered intravenously to the rat. *J. Biol. Chem.* 171:273-83.
- Cole, K. S. and C. L. Prosser. 1945. *Effects of product on a dog*. Monthly health report on problems related to product, sections H-I, H-II, H-III. Metallurgical Laboratory monthly report CN-2653, January 15, 1945, declassified April 28, 1952.
- Crowley, J., H. Lanz, K. Scott, and J. G. Hamilton. 1946. *A comparison of the metabolism of plutonium (Pu-238) in man and the rat*. Metallurgical Laboratory report CH-3589, May 31, 1946. [Changed from Official Use Only to unclassified on November 13, 1956.]
- Cunningham, B. B. 1972. In Seaborg 1972, pp. 17-20.
- Durbin, P. W. 1971. *Plutonium in man: A twenty-five year review*. UCRL-20850. Univ. of Calif., Berkeley, Calif.: Lawrence Radiation Laboratory.
- Durbin, P. W. 1972. Plutonium in man: A new look at the old data. Chapter 7.2 in *Radio-biology of plutonium*, eds. B. J. Stover and W. S. S. Jee, pp. 469-530. Salt Lake City: The J. W. Press.
- Durbin, P. W. 1976. What was going on at Crocker Laboratory when I landed there as a dishwasher and animal tender. Paper presented at the 21st annual meeting of the Health Physics Society held in San Francisco, July 1976. [Typescript from tape and slides kindly supplied by R. L. Kathren, Richland, Wash.]
- Fink, R. M. 1950. *Biological studies with polonium, radium, and plutonium*. National Nuclear Energy Series, div. VI, vol. 3. New York: McGraw-Hill.
- Finkel, M. P. 1947. The transmission of radio-strontium and plutonium from mother to offspring in laboratory animals. *Physiol. Zool.* 20:405-21. Also AEC report MDDC-750, January 28, 1947.
- Finkle, R. D., L. O. Jacobson, W. Kisielleski, B. Lawrance, E. L. Simmons, and R. H. Snyder. 1947. *The toxicity and metabolism of plutonium in laboratory animals*. Metallurgical Laboratory report CH-3783.
- Hamilton, J. G. 1944. *Metabolism of product*. Metallurgical Laboratory monthly report. CH-2383, October 15, 1944, declassified February 19, 1954.
- Hamilton, J. G. 1947. The metabolism of the fission products and the heaviest elements. Paper presented at a special symposium on the plutonium project at the 32d annual meeting of the Radiological Society of North America held in Chicago, December 1-6, 1946. *Radiology* 49:325-43.
- Hamilton, J. G. 1948. The metabolic properties of the fission products and actinide elements. *Rev. Mod. Phys.* 20:718-28.
- Kisielleski, W. and L. Woodruff. 1947. *Studies on the distribution of plutonium in the rat*. Metallurgical Laboratory quarterly report AECD-2009, August-November 1947.
- Langham, W. H. 1946. *Metabolism of plutonium in the rat*. LADC-472, declassified AECD-1914. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.

- Langham, W. H. and J. W. Healy. 1973. Maximum permissible body burdens and concentrations of plutonium: Biological basis and history of development. Chapter 12 in *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh, pp. 569-92. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.
- Langham, W. H., S. H. Bassett, P. S. Harris, and R. E. Carter. 1950. *Distribution and excretion of plutonium administered intravenously to man*. LA-1151. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory. [Reprinted as a landmark paper in *Health Phys.* 38:1031-60 (1980).]
- Lisco, H., M. P. Finkel, and A. M. Brues. 1947. Carcinogenic properties of radioactive fission products and of plutonium. *Radiology* 49:361-63.
- Muntz, J. A. and E. S. G. Barron. 1947. *Combination of plutonium with plasma proteins. Electrophoretic and chemical analysis*. Metallurgical Laboratory report CH-3757, AEC report MDDC-1268.
- Nickson, J. J., ed. 1945. *Report of conference on plutonium—May 14th and 15th*. Metallurgical Laboratory report CN-3167, July 23, 1945; declassification confirmed June 13, 1979.
- Norris, W. P. and H. B. Evans. 1946. *Studies on the metabolism and toxic action of injected radium*. Metallurgical Laboratory report CH-3852, June 1946, declassified AECD-1965, April 22, 1948.
- Painter, E., E. Russell, C. L. Prosser, M. N. Swift, W. Kisieleski, and G. Sacher. 1946. *Clinical physiology of dogs injected with plutonium*. Metallurgical Laboratory report CH-3858, June 1946, declassified AECD-2043, June 3, 1948.
- Perlman, I. 1972. In Seaborg 1972, pp. 26-27.
- Proescher, F. and B. R. Almquest. 1914. Contribution on the biological and pathological action of soluble radium salts II. *Radium* 3:85-95.
- Prosser, C. L. and M. N. Swift. 1949. *An interspecies comparison of the radiotoxicities of x-ray, Sr-89, and Pu-239*. Metallurgical Laboratory report CH-3893.
- Prosser, C. L., E. E. Painter, H. Lisco, A. M. Brues, L. O. Jacobson, and M. N. Swift. 1947. The clinical sequence of physiological effects of ionizing radiation in animals. *Radiology* 49:299-313.
- Russell, E. R. and J. J. Nickson. 1946. *The distribution and excretion of plutonium in two human subjects*. Metallurgical Laboratory report CH-3607.
- Schubert, J., M. P. Finkel, M. R. White, and G. M. Hirsch. 1950. Plutonium and yttrium content of the blood, liver and skeleton of the rat at different times after intravenous administration. *J. Biol. Chem.* 182:635-42.
- Scott, K. G., D. J. Axelrod, and J. G. Hamilton. 1949. The metabolism of curium in the rat. *J. Biol. Chem.* 177:325-35.
- Scott, K. G., D. J. Axelrod, H. Fisher, J. F. Crowley, and J. G. Hamilton. 1948a. The metabolism of plutonium in rats following intramuscular injection. *J. Biol. Chem.* 176:283-93.
- Scott, K. G., D. H. Copp, D. J. Axelrod, and J. G. Hamilton. 1948b. The metabolism of americium in the rat. *J. Biol. Chem.* 175:691-703.
- Scott, K. G., H. Fisher, D. Axelrod, J. Crowley, A. J. Barber, and J. G. Hamilton. 1944. *Metabolism of plutonium in rats*. AEC report MDDC-1018, October 15, 1944.
- Seaborg, G. T. 1944. Physiological hazards of working with plutonium. Memorandum to R. S. Stone, MUC-GTS-384, January 5, 1944. [Permission for quotation given to Dr. Langham in preparation of Langham and Healy 1973.]
- Seaborg, G. T. 1945. The chemical and radioactive properties of the heavy elements. *Chem. Eng. News* 23:2190-93.
- Seaborg, G. T. 1946. The transuranium elements. *Science* 104:379-86.
- Seaborg, G. T. 1949a. Place in periodic system and electronic structure of the heaviest elements. *Nucleonics* 5(5):16-36.
- Seaborg, G. T. 1949b. The eight new synthetic elements. *Science in Progress* 4, 6th series.
- Seaborg, G. T. 1963. *Man-made transuranium elements*. Englewood Cliffs, N. J.: Prentice-Hall.
- Seaborg, G. T. 1970. *Plutonium revisited*. AEC release S-34-70, October 8, 1970.

- Seaborg, G. T. 1972. *Nuclear milestones*. [A collection of speeches by G. T. Seaborg and colleagues on various occasions while Seaborg was chairman of the Atomic Energy Commission.] San Francisco: W. H. Freeman and Co.
- Seaborg, G. T. 1980. Personal interview in Berkeley, Calif., October 21, 1980.
- Seaborg, G. T., R. A. James, and A. Ghiorso. 1949. The new element curium (atomic number 96). Paper 22.2 in Seaborg, Katz, and Manning 1949, pp. 1554-71.
- Seaborg, G. T., R. A. James, and L. O. Morgan. 1949. The new element americium (atomic number 95). Paper 22.1 in Seaborg, Katz, and Manning 1949.
- Seaborg, G. T. and J. J. Katz, eds. 1949. *The actinide elements*. National Nuclear Energy Series, div. IV, vol. 14A. New York: McGraw-Hill.
- Seaborg, G. T., J. J. Katz, and W. M. Manning, eds. 1949. *The transuranium elements: Research papers*. National Nuclear Energy Series, div. IV, vol. 14B. New York: McGraw-Hill.
- Seaborg, G. T., E. M. McMillan, J. W. Kennedy, and A. C. Wahl. 1946. Radioactive element 94 from deuterons on uranium. *Phys. Rev.* 69:366-67.
- Snyder, R. H., W. Kisielski, and R. D. Finkle. 1949. *The toxicity and metabolism of plutonium in laboratory mammals*. Pt. III of Metallurgical Laboratory report CH-3783, AEC report MDDC-1140.
- Stannard, J. N. 1976. Plutonium toxicology and other toxicology. In *The health effects of plutonium and radium*, ed. W. S. S. Jee, pp. 363-72. Salt Lake City: The J. W. Press.
- Taylor, D. M. 1973a. Chemical and physical properties of plutonium. Chapter 9 in *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh, pp. 323-47. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.
- Taylor, D. M. 1973b. Chemical and physical properties of the transplutonium elements. Chapter 17 in *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh, pp. 717-38. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.
- Van Middlesworth, L. 1947. *Study of plutonium metabolism in bone*. AEC report MDDC-1022, declassified June 6, 1947. [Originally a Ph.D. thesis at the Univ. of Calif., Berkeley.]
- Werner, L. B. 1972. In Seaborg 1972, p. 24.

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Capsule Chronology^(a)

- 1946** Hanford establishes a Biology Section under Radiological Sciences Division (Parker, Kornberg, et al.).
- 1947** Hanford experiment on radioiodine in sheep begins; a multi-generational project (Bustad et al.). Continued for many years.
- 1947–1960** Work at Berkeley continues on numerous radionuclides by process of “chewing through the periodic table” (Hamilton and Durbin).
 Work on metabolism of ^{90}Sr in rhesus monkey (Durbin at Berkeley).
 Systematic study of lanthanides. Progression of behavior found from lighter to heavier elements (Durbin at Berkeley).
- 1947–1970 (approx.)** Long-term comparative toxicity experiment with mice at Argonne National Laboratory (M. Finkel et al.). A continuation of work begun during war; includes plutonium, radium, uranium, and fission products. Relative effectiveness is a function of dose. Soft tissue as well as skeletal tumors produced.
- 1950–1954** Work with tritium at Hanford. The earliest definitive experiments, including checks on man (Thompson, Ballou, and Kornberg).
- 1950** Utah project is organized. “Founding Fathers” gather, and staff is assembled. Los Alamos takes an active role in development of the project.
 Synthesis of berkelium (Thompson, Ghiorso, and Seaborg at Berkeley).
 Synthesis of californium (Thompson, Street, Ghiorso, and Seaborg at Berkeley).
- 1951 et seq.** Follow-up of Los Alamos plutonium workers begins (Langham, and Shipman; later Hempelmann and Voelz).
- 1952** Synthesis of einsteinium (Ghiorso, Thompson, Higgins, and Seaborg at Berkeley), discovered in products of first thermonuclear test. Kept secret until 1955.
- 1952** First beagle injected at Utah. Eight dosage levels settled on.
- 1952–1964** Long-term experiment at Argonne on ^{89}Sr , ^{90}Sr , and ^{90}Sr - ^{90}Y . Thousands of mice. Evidence for more than one process in tumor production. Ingested doses more effective than expected.
- 1953** Synthesis of fermium (Berkeley team). Same story as einsteinium.
- 1954–1958** Work at Berkeley on ^{223}Ra , the daughter of actinium. One of the few effects studies at Berkeley in the decade after the war (Durbin).
- 1954** Radioactive particles receive attention at Hanford (see chapter 9). Utah conference on plutonium, radium, and mesothorium (2nd Annual).
- 1956** Davis Project initiated; primarily to study effect of ingested ^{90}Sr but with radium injected to establish tie to Utah work. Tied closely to fallout problems. See chapter 13 (Anderson and Bustad; later Goldman et al.).
- Late 1950s** Experiment at Rochester on strontium in rats and monkeys (Tuttle and Casarett). For more on postwar work at Rochester see inhalation chapters.

(a) For inhalation work see chapters 9 and 10.

- 1954 et seq.** Systematic study of comparative metabolism of radionuclides, mostly fission products, at Los Alamos (Richmond and Furchner).
- 1955** Synthesis of mendelevium (Ghiorso et al. at Berkeley).
- 1955** First osteosarcoma in the Utah experiment.
- 1956–1984** Continuous work at Hanford (later Pacific Northwest Laboratory) on gastrointestinal uptake and effects of radionuclides in gut (Sullivan).
- 1958** Synthesis of nobelium (Ghiorso et al. at Berkeley).
- 1958–1984** Effects of age on metabolism of radionuclides. Radiobiology of fetal and juvenile mammal (Sikov at Hanford).
- 1959** Large feeding experiment with ⁹⁰Sr begins with miniature swine at Hanford; see chapter 13 (McClellan and Bustad).
- 1959–1964** Metabolism of strontium in the dog (Norris et al. at Argonne).
Skin tumors found.
- 1960** Miniature swine at Hanford enter the radioiodine experiment.
- 1960s** Metabolism of americium and radiocalcium in the rat (Durbin at Berkeley).
- 1961** Lovelace Project established (see chapter 9).
Ten-year-anniversary symposium of Utah Project (Jee et al. 1962).
Synthesis of lawrencium (Ghiorso et al. at Berkeley).
Retention functions worked out in the Utah beagles.
- 1962** Plutonium studied in swine at Hanford (Bustad et al.).
First Hanford biology symposium is on transuranium elements.
- 1963** Second Hanford biology symposium is on radioiodine.
- 1965** Binding of plutonium to body constituents worked out (Taylor).
- 1965 et seq.** Transplutronics found to be less toxic in general than plutonium.
- 1966** Americium added to the Utah experiment.
- 1967** RBE^(a) of radionuclides in Utah experiment appears to be grossly similar to that found earlier in mice at Argonne.
Importance of liver deposition of plutonium and thorium again surfaces.
- 1967** Fifteen-year-anniversary symposium of Utah Project (Mays et al. 1969).
- 1970** Twenty-year-anniversary symposium of Utah Project (Stover and Jee 1972).
- 1970s** Work at Colorado State University on entry of plutonium via wounds (Lebel, Watters, et al.).
- 1971** Radiostrontium symposium held at Davis (Goldman and Bustad 1972).
- 1971–1972** Review of plutonium in man using primarily the patients injected during World War II (Durbin at Berkeley).

(a) For abbreviations and acronyms, see Appendix D.

- 1973 Definitive reviews of biomedical aspects of plutonium and the trans-plutonic elements. Book edited by Hodge, Stannard, and Hursh. Reviews by Bair and colleagues; Dolphin; Durbin; Ghiorso, Langham, and Healy; Low-Beer; Parker; Seaborg; Stannard; Taylor and Vaughan. (Note: reviews of uranium are contained in chapter 2.)
- 1974 Real differences noted between ^{238}Pu and ^{239}Pu in metabolism and effects (Bair et al. at Hanford).
AEC develops series of in-house task forces on actinides centered especially on adequacy of standards for plutonium.
- 1974 Emphasis on plutonium in gonads (Utah, Los Alamos).
Comparison of plutonium isomers at Hanford (Bair).
- 1975 Twenty-five-year-anniversary symposium of Utah Project (Jee 1976).
- 1977 ERDA sponsors a workshop at Seattle on the actinides. Plans laid for many years.

Chapter 8

Post-World-War-II Research on the Actinides and Fission Products

Overview

This chapter reviews an effort that could easily be a book in itself. In fact, some full-sized books exist that consider only a part of the subject matter embraced by this chapter. Despite efforts to be concise, it must perforce be rather lengthy, even with postponement for later consideration of inhalation toxicology and studies primarily centered on research generated by the problems of fallout from nuclear weapons tests (chapters 9, 12, and 13).

Some of the active laboratories of World War II blossomed forth with major efforts, which were largely extensions of their war work (Extensions and Consummations). Entirely new projects of considerable size were set up to address specific areas of major concern (New Projects: The King-Sized Experiments). Laboratories that were primarily focused on practical or industrial-type problems during the war expanded their horizons so materially that the work was "almost new," even if rooted in their wartime problems (Almost New Projects: Hanford and Los Alamos). Other laboratories in the United States participated to a lesser degree, largely because of involvement in other areas (Other U.S. Work).

Although this book emphasizes U.S. work, since it is a history and not a monograph, it is essential to take up briefly what was going on in other countries, particularly the United Kingdom, France, and the USSR (Work Abroad).

The organization of the chapter is by laboratory in order to permit a connected discourse on how the several groups attacked the problems they chose to focus upon. Each had its own philosophy and approach, even though the ultimate facts emerging were more or less consonant with each other.

One area, the transplutonic elements, is handled differently. Small glimpses of work with the elements above plutonium in the periodic table are seen from time to time in reviewing the individual laboratories. But there was no single effort with the transplutonics comparable to those with plutonium or the fission products. Therefore, it was considered advisable to develop a short overview of the biomedical work done in several laboratories with transplutonics in animals as a final section (The Transplutonic Elements).

Support for biomedical studies of the actinides and fission products was especially strong during the years from 1950 to 1975. It has continued but with diminishing strength into the 1980s. Large experiments were organized and supported because they had to be done. They must be continued to their logical conclusions. This support benefited all areas of radioisotope toxicology and will have, if the lessons learned are heeded, a significant impact on the field of chemical toxicology. For these reasons, and despite the fact that some of the motivation came from the problems of fallout, which many would prefer we had never had to face, I have labeled these efforts "part of a Golden Era."

I. Part of a Golden Era

The wartime efforts had established many basic facts about the behavior and effects of the fission products and the actinide elements. But much remained to be done, particularly in finding the effects of low-level, long-term exposures. While true in nearly all of the areas of interest in this book, these needs were especially evident in the domains of the new dimensions of internal emitter research discussed in the last two chapters.

The explosion of knowledge in the postwar years applied in its way to the research on internal emitter effects and metabolism. The pressures were easing so that mechanisms could be explored in depth along with the more practical needs for low-level and long-term study. While the enterprise got a further boost from the problems attending the development of nuclear power and fallout from nuclear weapons testing (see chapters 11, 12, and 13), it had considerable momentum already from the unfinished business of the war years. This took the form of direct extensions of work already under way and in the organization of new projects to address the chronic toxicity question, with fully sanctioned forays into the exploration of mechanisms (up to a point). We will concentrate on the first two approaches in this chapter and leave some of the more basic considerations for chapters 20 and 21 or, alas, leave them out altogether since they have been very well covered in the published literature. Even with this restriction, we will not be able to examine what was done in anything like the detail accorded some other areas. There has been so much done and so much published that detailed examination would require far too much space. Fortunately, there have been numerous symposia and published volumes so that pursuit of further information is much easier than in some of the other areas pertinent to our objectives. These publications will be referenced at appropriate points.

In terms of both financial support and interest in the biomedical community, these years, 1950 to 1975, were in a way a Golden Era for internal emitter research, as they were for all of radiobiology. Experiments were organized and most will be completed that neither could nor would be undertaken in the 1980s. It is said that the pertinent Congressional Committees even asked the Director of the Division of Biology and Medicine of the Atomic Energy Commission (AEC) if he was sure he had asked for enough money to do what needed to be done! Indeed a Golden Era.

II. Extensions and Consummations

In this section, we will examine research on fission products and the actinides that is clearly a direct extension of wartime experiments or so closely tied

thereto as to be so characterized. Much of this work culminated in the decade of the 1950s and was supplanted by the newly organized or reorganized projects to be viewed in section III.

A. Argonne National Laboratory

1. Relative Toxicity in the Mouse

The comparison of acute lethality of radium and plutonium in rat and mouse at Chicago and Rochester was discussed in chapter 7. No further comparative toxicity work was done at Rochester, but at Argonne National Laboratory (ANL), the standardized radioisotope toxicity experiments^(a) reported early by Brues et al. (see chapter 7) were carried forward by Miriam Finkel and her colleagues. The result was a series of detailed papers in ANL reports and many published documents. Some of these were called "Relative Biological Effectiveness of Internal Emitters."^(b)

One of the most concise reports is that by M. P. Finkel (1956). Here, 6,254 mice contributed data for the twelve isotopes listed in table 8.1. The important characteristics of the isotopes used are shown in table 8.2:

TABLE 8.1. Materials and Range of Doses

Isotope	Range of Doses ($\mu\text{C/gm.}$)	No. of Dose Levels	No. of Mice
Ra ²²⁶	4.170 - 0.0006	14	675
Pu ²³⁹	0.0504 - 0.00004	12	765
Po ²¹⁰	0.097 - 0.00046	9	645
U ²³³	0.10 - 0.001	10	675
U ²³²	0.001 - 0.0001	3	135
Th ²²⁸	0.360 - 0.0066	6	75
Ru ^{106*}	8.94 - 0.57	5	40
Sr ⁹⁰	9.33 - 0.001	12	810
Sr ⁸⁹	7.8 - 0.05	7	352
Y ⁹⁰	28.9 - 4.7	10	103
P ³²	7.36 - 0.01	8	401
Ca ⁴⁵	49.6 - 0.016	10	448
Controls			1,130
Total			6,254

*From the work of Walton and Brues.

Source: Reset from M. P. Finkel 1956. Note use of original terminology. Reprinted with permission of Radiological Society of North America, Oak Brook, Illinois, copyright 1956.

(a) Conceived and designed by Miriam P. Finkel (personal interview, 1978).

(b) This broad use of the term "relative biological effectiveness" (RBE) disturbed some who thought the term should be reserved for comparison of the effects of radiation with different linear energy transfer (LET) values. The usage persists in some segments of the internal emitter literature. However, the International Commission on Radiological Protection (ICRP) and others use the term "equal effectiveness ratio." This author prefers the latter since RBE has a different and earlier specific definition.

TABLE 8.2. Characteristics of the Isotopes Used in the Standardized Radioisotope Toxicity Experiments at Chicago (ANL)

Isotope	Energy (MeV)	Half-Life	Subsequent Radiations	Site of Major Deposition
Ra ²²⁶	4.8 α	1620 yr.	4 alphas within 4 days	Skeleton
Pu ²³⁹	5.15 α	24,300 yr.	(U-235, 7.1 x 10 ⁸ yr.)	Skeleton, liver
Po ²¹⁰	5.3 α	138.3 days	(stable lead)	Reticular tissues
U ²³³	4.8 α	1.62 x 10 ⁵ yr.	(Th-229, 7,300 yr.)	Skeleton, kidneys
U ²³²	5.3 α	70 yr.	5.4 α , 1.9 yr.; 4 alphas within 4 days	Skeleton, kidneys
Th ²²⁸	5.4 α	1.9 yr.	4 alphas within 4 days	Reticular tissues
Ru ¹⁰⁶	0.04 β^-	1 yr.	3.5 β^- , 30 sec.	Skeleton, liver
Sr ⁸⁹	1.48 β^-	50 days	(stable Y)	Skeleton
Sr ⁹⁰	0.54 β^-	28 yr.	2.18 β^- , 64.2 hr.	Skeleton
Y ⁹⁰	2.18 β^-	64.2 hr.	(stable Zr)	Skeleton, liver
P ³²	1.70 β^-	14.3 days	(stable S)	(General), skeleton
Ca ⁴⁵	0.25 β^-	152 days	(stable Sc)	(General), skeleton

Source: Reset. from M. P. Finkel 1956. Reprinted with permission of Radiological Society of North America, Oak Brook, Illinois, copyright 1956.

In addition to presenting the acute toxicity of many isotopes not ready for presentation at the end of the war years, this work extends into the area of chronic toxicity, especially induction of lymphoid and bone tumors. The acute mortality, expressed as a rate per one hundred mice per twenty-five-day interval, is shown in figure 8.1.

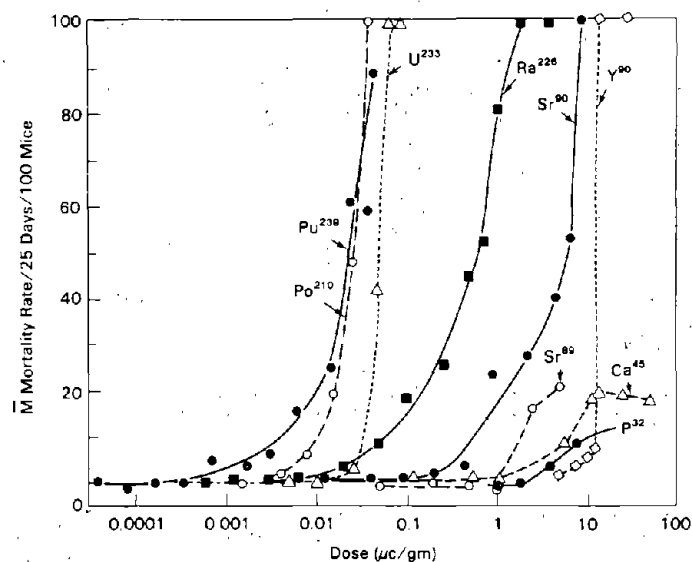


FIGURE 8.1. Relationship between isotope dose and mortality rate in mice. (Redrawn from M. P. Finkel 1956. Reprinted with permission of Radiological Society of North America, Oak Brook, Illinois, copyright 1956.)

Obviously, plutonium, polonium, and even ^{233}U are considerably more effective than ^{226}Ra ^(a), while the beta and beta-gamma emitters are much less effective. This confirms and amplifies the plutonium/radium relationship discussed in chapter 7. The time to 50% mortality showed roughly the same relationship in this more extensive study.

These same data, plotted as a "relative biological effectiveness" factor (see discussion above) by converting the radium curve to unity, are shown in figure 8.2.

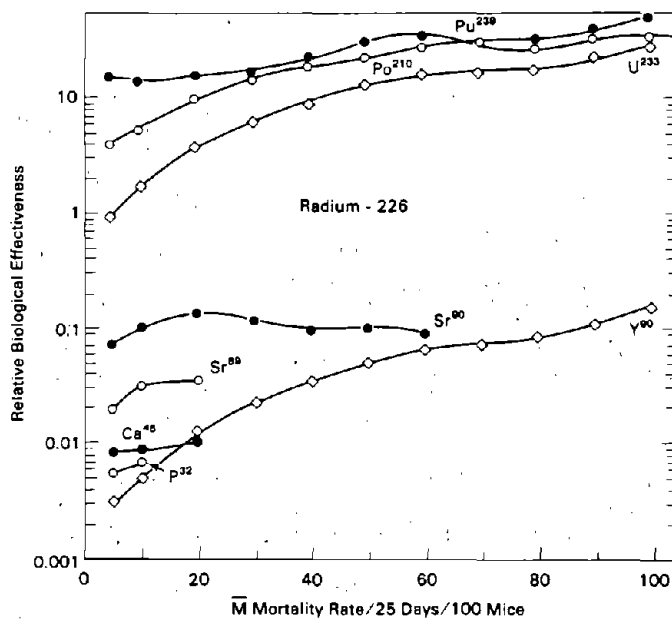


FIGURE 8.2. Biological effectiveness relative to radium in increasing net mean mortality rate in mice. (Redrawn from M. P. Finkel 1956. Reprinted with permission of Radiological Society of North America, Oak Brook, Illinois, copyright 1956.)

These figures must be regarded as somewhat tentative since the last animals had not yet died and the experiment was thus incomplete. Nevertheless, it is quite clear that the RBE varies with the mortality rates, a point of importance for extrapolation to the very low doses in human exposure situations. The author gives ratios of mortality at the lowest measured rate of 15(^{239}Pu) : 4(^{210}Po) : 1(^{226}Ra) : 0.07(^{90}Sr) : and 0.02 (^{32}P).

Turning to tumor incidence, we find this influence of dose and time even more clearly evident. The incidence of *lymphoid tumors*, taken again as a rate per one hundred mice per twenty-five-day interval, is relatively low for the bone-seeking elements and much alike except for ^{45}Ca at high doses. But the soft-tissue-seeking alpha emitter, ^{210}Po , assumed considerable importance at

(a) See chapter 2 for further discussion of the $^{233}\text{U}/^{226}\text{Ra}$ story.

about $0.01 \mu\text{Ci/g}$ administered dose, while the soft-tissue-seeking beta emitters such as ^{32}P and ^{90}Y became quite potent generators of lymphoid tumors at doses above about $1 \mu\text{Ci/g}$.

All of this is shown in figure 8.3.

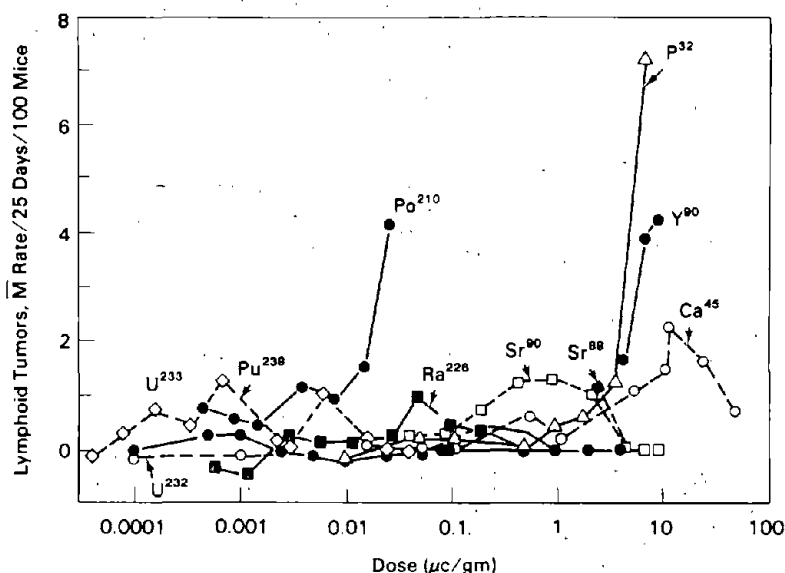


FIGURE 8.3. Relationship between isotope dose and net rate of mortality with lymphoid tumors in mice. (Redrawn from M. P. Finkel 1956. Reprinted with permission of Radiological Society of North America, Oak Brook, Illinois, copyright 1956.)

By contrast, the alpha emitters plutonium and radium increased the rates of bone malignancy at doses in the range of approximately 0.002 to $0.02 \mu\text{Ci/g}$ for plutonium and 0.008 to $0.7 \mu\text{Ci/g}$ for radium (as read from the graphs), while the beta emitters became effective only at high doses. These relationships are shown in figure 8.4.

If an average rate of incidence of ten deaths with bone tumors per twenty-five days per one hundred animals is taken, the effectiveness ratios become $20(^{239}\text{Pu}) : 1(^{226}\text{Ra}) : 0.2(^{90}\text{Sr}) : 0.1(^{89}\text{Sr}) : 0.05(^{45}\text{Ca})$. While not identical with the ratios derived from the mortality data, the complexities of the experiments are such that these must be regarded as more like them than different.

At one of the M. D. Anderson Hospital cancer symposia in Houston, M. P. Finkel presented a summary paper involving some of the same basic data but expanding more upon possible mechanisms of the differences in toxicity of the several isotopes. The paper was published in 1959 (Finkel 1959a). The incidence rates were translated to a probability that the animal will die with a malignant bone tumor. Both the effectiveness ratios and the relationship to dose remain essentially as before, with plutonium clearly the most potent bone carcinogen at low doses and ^{90}Sr and ^{45}Ca the most effective at high doses. A possible explanation is that the alpha particles kill more cells at all dosages, and optimal neoplastic changes thus occur at lower doses of these. The beta emitters by

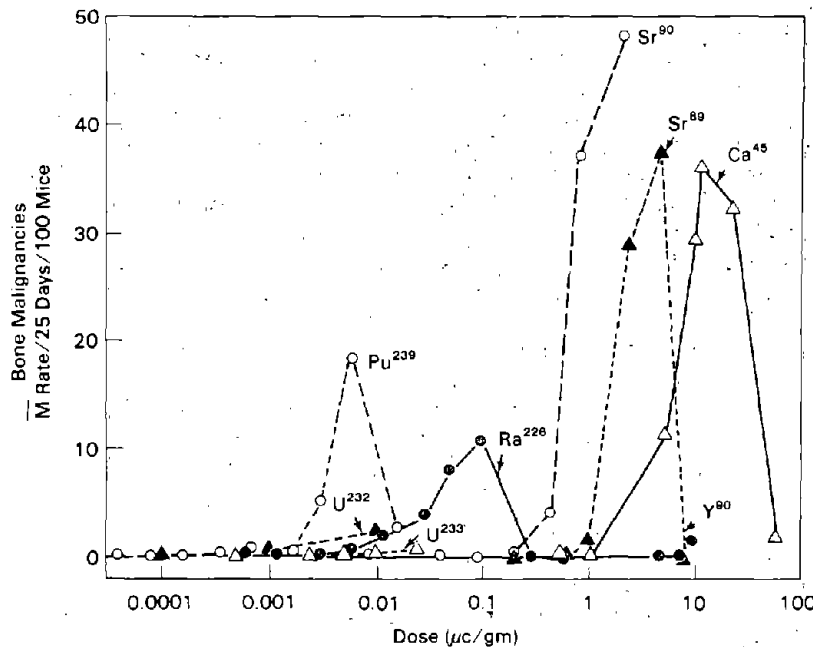


FIGURE 8.4. Relationship between isotope dose and net rate of mortality with malignant bone tumors in mice. (Redrawn from M. P. Finkel 1956. Reprinted with permission of Radiological Society of North America, Oak Brook, Illinois, copyright 1956.)

contrast may be less effective carcinogens at low doses and also produce less cell killing. Thus, many potentially neoplastic cells are alive when the beta doses finally reach carcinogenic levels.

An effect of dosage pattern is seen with strontium isotopes. This is summarized in the Texas paper but is given in much more detail in a series of ANL quarterly reports, which we will review in the next section.

The importance and behavior of the latent period for cancer induction, a ubiquitous problem in all of cancer biology, was, of course, considered in this long series of experiments at Argonne. The first impression (during the war years) was that the period of latency increased with decreasing dose. With the more extensive data available, the latent period gradually appeared to decrease to about 150 days and to be independent of dose. Indeed, it appeared to be independent of age, of isotope, and perhaps even of species.^(a)

(a) That this is probably not a generalized phenomenon for all forms of cancer is apparent from the masterful review of the pathogenesis of radionuclide-induced tumors given by Casarett at the 1972 Hanford symposium, *Radionuclide Carcinogenesis* (Casarett 1973). There is the puzzle about how to define latent period. The Argonne workers chose to define it as the time between isotope administration and death with a tumor. Later work with serial x-ray studies of the skeleton (to be discussed) requires a different definition. Another view is that there are two periods: (1) the time between the initiation of the carcinogenic process and its expression in some detectable form,

In another 1959 summary paper involving 4,616 mice, Finkel (1959b) presents data for six of the twelve isotopes presented in the 1956 paper. The same general relationships are seen for decrease in average survival time (figures 2 and 3 of the referenced paper) as in the earlier reports.^(a) Tumor expectancy is given instead of tumor incidence. This is based on the number of tumors still to appear in a population divided by the number of animals still alive at any given time—the calculation obviously being done after the data were in. This has the advantage of not being influenced by past events, but the disadvantage that each surviving fraction of the surviving population has less time to live and thus less time to develop tumors. But the parameter can be manipulated to produce an entity called “tumor intensity.”

Using this and other parameters, Finkel concludes that tumor induction may be a more sensitive indicator of radiation damage than mortality. Also, by analysis of the accumulating information on soft-tissue tumors, she suggests that these (e.g., reticular tissue tumors) may be a more sensitive indicator even than bone-tumor incidence.

The toxicity ratios shown, but not discussed in this last series of experiments, appear similar to those found earlier.

In essence, the primary information derived from these long-term experiments is a much strengthened toxicity ratio for plutonium/radium. It also supports ratios for many other isotopes, and provides some leads toward concepts and mechanisms. On balance, the ratios used by Brues at the time of the first Tri-Partite Conference on Internal Emitter Standards in 1949 look reasonably correct with ten years of added perspective (chapter 16).

Because of the ubiquitous problems with endemic disease in the animal colony of the Plutonium Project (old Site B discussed in chapter 2 and Appendix B) and even after the war, Finkel and her colleagues did an entirely new radium experiment during the 1950s and 1960s. This was discussed briefly in chapter 2 (see Finkel, Biskis, and Jinkins 1969). The new experiment can be plotted on the same mortality scale as used in the earlier work, i.e., fraction of mice bearing at least one malignant bone tumor against accumulated radiation dose at one hundred days. In the reanalysis of both sets of data by Durbin and Wrenn (1975), discussed in chapter 2, the slope of the curve for the new experiment is 0.043% tumors/rad versus 0.012% tumors/rad in the 1953 experiment.

and (2) the time between the delivery of the effective radiation dose and the completion of the pathologic processes required to start the carcinogenic response. In practice, the so-called latent period may often include both of these. But techniques of detection and measurement will have a sharp influence. Age must have an effect if the radiation dose is given late enough in the life span. Later Argonne work addresses all of these factors plus a lot of information on the role of cofactors (e.g., viral components in the etiology). But it is significant that the results of one of the largest and most complete studies in the mouse up to its time indicated relative independence of the latent period from several important factors usually expected to have an important influence. Finkel (1981) prefers to view the phenomena as illustrating only that the probability of getting bone cancer increases with increasing dose.

- (a) The same animals were involved in these two reports. The difference in total numbers of mice is due to omission of a few high-dose groups. The isotopes were not all studied simultaneously because of space limitations. Radium and plutonium were done together; the uranium isotopes were done together. Polonium was done separately.

Apparently the clearing out of endemic infection saved the animals for bone tumor development! Whether or not the toxicity ratio would be altered under these different laboratory conditions cannot be stated and probably will never be known. The simplest procedure is to assume that all incidence curves at the chronic level would be moved in the same direction in the new animal care environment, and their relationship to each other would remain roughly the same. This emphasizes the extent to which intercurrent murine infections have been a cross to bear in long-term work, and the importance of having the best and constant quality of animal housing and care.

In summary of these experiments, the following generalizations can be made:

1. The toxicity ratio is a function of the magnitude of the carcinogenic effect. At very low doses, ^{239}Pu appears to be only about five times as potent as ^{226}Ra , while ^{232}U is about twice as effective. At these same low doses, ^{233}U is one-half as effective as ^{226}Ra , while ^{90}Sr and ^{45}Ca are 1/125 and 1/1000 as effective, respectively. These are all on the basis of bone-tumor development. In the high-dose domain, ^{90}Sr and ^{45}Ca become much more effective; indeed, these produced the maximum number of tumors, probably because the alpha emitters have a much higher component of cell killing.
2. The toxicity ratio for mortality is not identical to that for carcinogenesis, but it is roughly comparable.
3. There is an indifference range where effects are no greater than in controls. No linear function could be made to fit the incidence data, especially at low doses. The authors could not conclude that a threshold existed without an even larger number of animals.
4. The latent period for cancer induction in these experiments seems to be independent of isotope and size of dose, but this is not certain.
5. Soft-tissue tumors were induced by all of the isotopes but especially by ^{210}Po , ^{90}Y , and ^{32}P . These tumors may turn out to be as sensitive an indicator as bone tumors.
6. The injected-dose basis is used in this work because the authors feel that more information is needed before radiation dose can be calculated with confidence.

2. Radiostrontium in Mice

As part of the large Argonne effort with mice, particular emphasis was placed on work with both ^{89}Sr and ^{90}Sr , and the ^{90}Sr - ^{90}Y couplet. The results were seen first in Quarterly Progress Reports (Finkel, Brues, and Lisco 1952, 1954; Finkel, Lisco, and Brues 1954, 1955; Finkel et al. 1956), and somewhat later in published papers (Finkel, Biskis, and Scribner 1959; Finkel, Biskis, and Bergstrand 1960; Finkel, Bergstrand, and Biskis 1960, 1961; Finkel, Jinkins, and Biskis 1964). This was a major effort involving thousands of mice to whose care Dr. Finkel, along with a dedicated staff, devoted herself personally. Although nominally a part of the relative toxicity series, these went well beyond its needs. In part, the effort was enhanced by the problems of fallout and, in part, by the need for careful dissection of the relevant parameters.

There are many progress reports and a few additional published documents beyond those cited in the bibliography. But those cited give the flavor of what was done, and going much further would carry us too far beyond studies to be regarded as direct extensions of the war work.

It will be noted that the cited ANL documents concern ^{89}Sr , while all of the publications refer to ^{90}Sr . The Argonne group places little emphasis on this difference, and it must be concluded that, except for some temporal aspects, the differences between the two isotopes were small.

Two major questions were addressed in these experiments: (1) the influence of dosage parameters brought about by giving single compared to divided doses, and (2) mechanistic studies, including general and special pathology.

In the comparison of dosage regimes, it is pointed out that dose fractionation does more than modify dose rate. Deposition is apt to be more uniform in bone on a split-dose regime since there are many more deposition sites available. By dividing the doses among regimes of one, five, or twenty injections and the isotope doses over a suitable range, many combinations of doses and dose rates could be obtained. The results are complex, but a few points can be extracted.

1. Life shortening was, in general, less with multiple doses, but the difference was small at low doses. This is illustrated in figure 8.5 where expectation of life in the mouse given by Finkel, Biskis, and Bergstrand (1960) and Brues (1949) is plotted against dose. (These data were recalculated by Stannard, Blair, and Baxter [1964].)

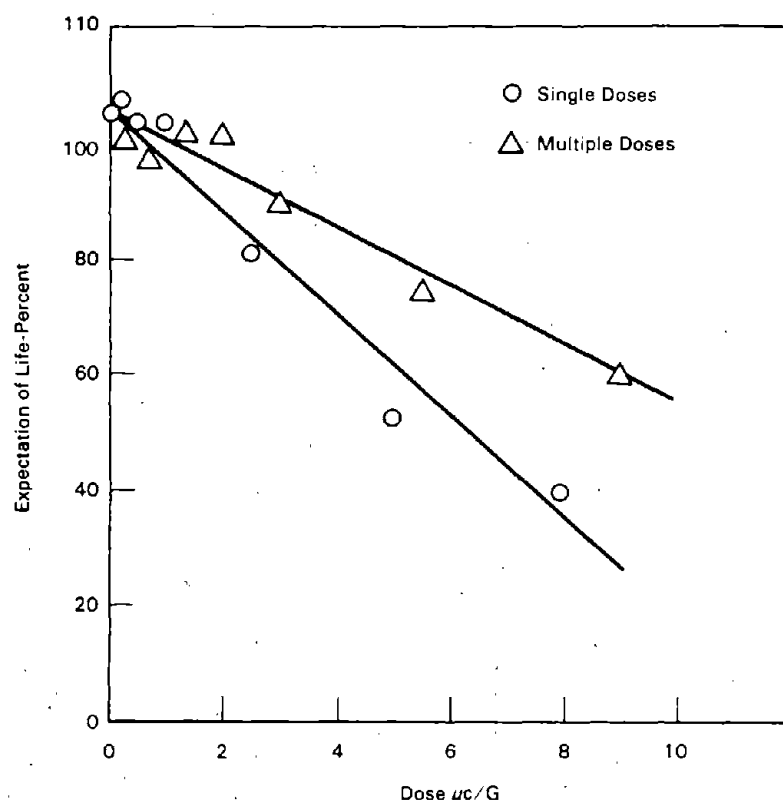


FIGURE 8.5. Life-span shortening with multiple doses of ^{90}Sr . (Redrawn from Stannard, Blair, and Baxter 1964, based upon data of Finkel et al. over several years. Reprinted with permission of Academic Press, Inc., Orlando, Florida, copyright 1964.)

2. The incidence of malignant bone tumors is a more complex function of dosage regimes. This is illustrated in figure 8.6, taken from Finkel, Biskis, and Bergstrand (1960). In general, the incidence of osteogenic sarcoma was higher at most times after the single injections. But the difference is very small at the highest dose and reverses itself at about 375 days at the middle dose. At the low dose of most interest to radiation protection, the greater effectiveness of single doses is quite clear. Whether this difference resides in the presence of recovery from the low-LET beta radiation, mode of deposition, isotope removal rates, or some combination of these cannot be determined from the information at hand.

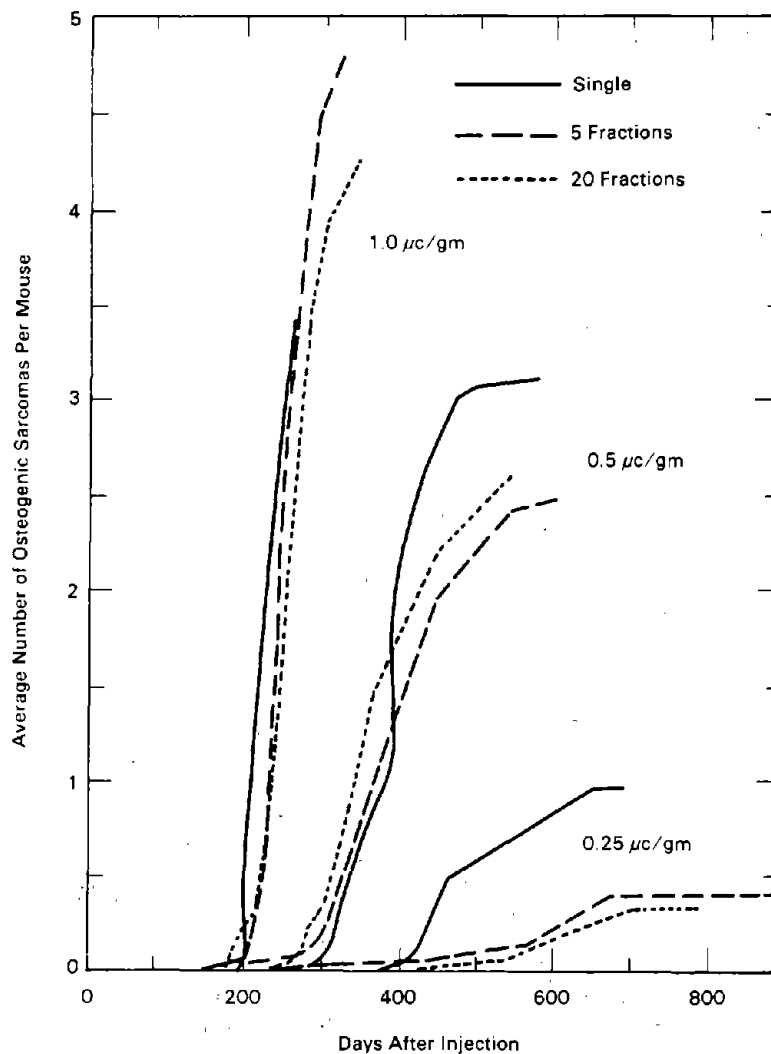


FIGURE 8.6. Incidence of osteogenic sarcomas in mice as a function of time and dosage pattern of ^{90}Sr – ^{90}Y . (Redrawn from Finkel, Biskis, and Bergstrand 1960. Reprinted with permission of University of Minnesota-Twin Cities, Minneapolis, Minnesota, copyright 1960.)

3. Tumors of the blood-forming tissues depend in a complex way on total dose and fractionation. For example, a dose of 1 $\mu\text{Ci/g}$ was most effective in producing lymphocytic neoplasm if given in a single injection, least effective if divided into twenty parts. At 0.5 $\mu\text{Ci/g}$, there was little difference between a single dose and five fractions, but twenty fractions were less carcinogenic than either a single or five. At 0.25 $\mu\text{Ci/g}$, both five-part and twenty-part fractionations were more effective than a single injection. This contrasts with the mortality and bone-tumor-incidence figures.
4. Explanation of the findings in (2) and (3) was considered to lie in the presence of at least two, perhaps more, processes. One may be a direct effect of the radiation; another may be indirect (part of the multifactorial causation of cancer?) or abscopal.
5. The authors propose that many of the data are consistent with the idea that initial dose rate is an important, perhaps controlling, factor.
6. There are definite strain differences in both the incidence and the location of tumors.

Other work of the Argonne group showed that autoradiography could be used for dosimetry as well as microlocalization of the isotopes (Marshall, Rowland, and Jowsey 1956; Rowland and Marshall 1959; Marshall and Finkel 1960). Also, serial x-ray examinations permitted early detection of tumors long before anything could be palpated. This was extended at both Argonne and other laboratories into considerable formal study of the kinetics of tumor growth.

The consequences of continuous ingestion of ^{90}Sr were not quite as expected (Finkel, Biskis, and Bergstrand 1960; Finkel, Bergstrand, and Biskis 1960). Strontium is reasonably well absorbed from the gut, i.e., about 30% of administered dose. Yet, animals fed a ^{90}Sr - ^{90}Y mixture (the ^{90}Y is essentially unabsorbed) from conception showed surprisingly few tumors except at quite high doses. This was despite some life-span shortening. Those sarcomas that did appear were later as well as less numerous than after injection. This was considered a dose-rate effect. Also, there was little evidence that neonatal and young animals were significantly more sensitive than adults on the basis of the parameters measured.

3. Other Work at Argonne

Several other studies in the decade and a half after the war fall into the category of this section.

a. Lethality and Carcinogenicity of Radiostrontium in Other Species

Other species, such as dogs and cats, were occasionally added to the strontium studies by the Finkel group and described in some of the publications cited. A quite complete report of work with the dog is contained in the symposium, *Biomedical Implications of Radiostrontium Exposure*, held at the Davis, California, laboratory in 1971 (Finkel et al. 1972). This work started in 1947. It differed from the studies at Utah, which we will review in the next major section of this chapter, by including multiple injections from birth as well as single injections. There were 147 dogs with 29 controls in a complex mixture of intravenous, subcutaneous, and placental dosage regimes and from 1 to 259 injections. The results were qualitatively comparable to the results with mice, except for a greater incidence of tumors of bone other than osteogenic sarcomas such as hemangiosarcomas, fibrosarcomas, and chondrosarcomas. The incidence of

these was up to one-fourth in the dog versus low and not related to dose in mice. Strontium-90-yttrium-90 is absorbed in the larger bones of dogs, and thus a given injected dose produces more rad than in the small bones of mice.

The primary idea of this work was to help scale from mouse through dog to man. The conclusions are that, with proper corrections for size, retention, etc., dog and mouse are probably equally sensitive, young animals are not more sensitive than adults, and a dose distributed nonuniformly in space and time is more oncogenic than a uniformly distributed dose. These last two conclusions are somewhat contrary to general radiobiological thinking and should receive further scrutiny.

b. Metabolism of Strontium

Decker and Norris developed a device for measuring the gamma radiation from ^{85}Sr in the dog (Decker and Norris 1959). This was used, along with an ionization chamber set up for rodents, to investigate strontium metabolism as a function of age (Speckman and Norris 1964; Decker, Kaspar, and Norris 1964). The ^{85}Sr was produced at the laboratory by deuteron bombardment of rubidium chloride. The animals in the first study were rats and a few mice, in the second study dogs.

The power function so characteristically found to describe retention of bone seekers in experiments at Chicago seemed to describe the data for mice injected at 271 days and rats injected from 207 days onward. Injection at earlier times gave curves with changing slope up to a time that varied with the age at injection. All the retention curves in the rodent showed identical slopes after about 100 days. Mathematical treatment of the data is indulged in.

In the dog, only a modified power function could describe the retention data. Strontium retention became progressively less up to an age approaching ten years. But the difference was small after five years. Possible mechanics are discussed in somewhat more complex fashion than we saw in the handling of the radium data (chapter 1).

Brues et al. made a special effort to look at the retention and metabolism of ^{90}Sr in soft tissues since tumors were arising in these, and, in their view, the subject had been neglected (Brues et al. 1967). This work was part of an international symposium concerned with fallout problems that we will examine presently. But it can be considered also an extension of the Plutonium Project work. The object was determination of dosage, which they put in terms of microcurie-days. Particular emphasis was placed on blood and testis. There were two experiments: one in which the strontium was accompanied by its yttrium daughter, the other in which the ^{90}Sr had been freed of ^{90}Y before injection. The $^{90}\text{Y}/^{90}\text{Sr}$ ratio was different in different tissues and at different times. Liver had the highest ratio for the longest time. The work indicated that dosage calculations to soft tissues would not be simple.

Other kinetic studies compared plutonium and yttrium in blood, liver, and skeleton in the rat (Schubert et al. 1950); relative rates of transfer of barium, radium, and strontium between blood and bone (Lloyd 1968), this time including data on man, rabbit, and rat. The first was aimed primarily at further understanding of the role of radiocolloids and of a diffusion-controlled mechanism in uptake by bone, which obediently followed diffusion kinetics except for an initial, very rapid process, which was not kinetically like diffusion. The second work bore more on the discrimination factors seen in many physiological processes, which we will review in chapters 13 and 15.

c. Locally Deposited Isotopes

Even during the war years, the Chicago group was interested in induction of tumors of the skin by placement of beta-irradiating sources of different geometries. In the postwar period, this was extended to studying local effects of an insoluble beta emitter placed under the skin of the back or in a limb. Finkel et al. (1956) used a suspension of $^{91}\text{YPO}_4$. Local lesions included greying of the fur, epilation, ulceration, skin carcinoma, and other tumors near the site of injection. In addition, osteogenic sarcomas appeared at the highest dose, as did diseases of kidney, liver, and lung (including lung tumors). Many of these, however, were due to endemic infections in the colony, but some might have been due to radioisotope absorption from the injection site. The injected doses were quite large.

This initial study was followed some years later by a series issued by Brues and collaborators under the title *Mechanisms of Carcinogenesis*. The central theme was to define the conditions under which tumors are induced by local irradiation (Brues et al. 1966–1969; Brues et al. 1967). They also used chemical carcinogens. In so doing, they learned much about the transfer of isotopes from injection sites, cell dynamics preceding and during the carcinogenic process, role of various physiological variables including hormonal controls, etc. Further discussion would carry us beyond the scope of this chapter. Suffice it to say that this progression is fairly typical of how the programmatic war work gradually metamorphosed into studies of fundamental mechanisms. The same is true of Miriam Finkel's work, which became more and more oriented to fundamental cancer biology after the early 1960s.

d. Plutonium at Argonne National Laboratory in the Postwar Years

Whereas Chicago was the major center along with Berkeley for plutonium research of all kinds during the war years, it eased up greatly in the postwar era, particularly in biology and medicine. Other laboratories were picking up the thread with large-scale biology experiments. The primary contributions from ANL came from the relative toxicity work already described (a not inconsiderable effort) and occasional publications and papers at symposia. One of the papers concerned a study of plutonium toxicity in nine hundred mice (Finkel and Biskis 1962). This gives in detail the story of the plutonium segment of some of the earlier, more general, publications.

The findings are by now a somewhat familiar story, but the doses went lower than in the early work, and the analysis of the findings is most complete. Liver changes were quite common (fatty and parenchymatous degeneration, inclusion bodies, but no malignant tumors). Osteogenic sarcomas appeared in 66 of 886 mice studied. There was a maximum in average tumor expectancy at a dose above the median dose, but not the highest, i.e., $6.3 \mu\text{Ci/kg}$, while the dose range was 0.04 to $40.6 \mu\text{Ci/kg}$, given intravenously. The tumor expectancy was linear to dose only on a logarithmic plot.

An interesting summary and indication of how the various end points move about with dose is found in table 8.3, taken from the cited reference.

Because of the interest in environmental contamination in the 1960s and 1970s, Finkel dusted off and reanalyzed some experimental data obtained during the war years concerning transfer and effects of plutonium in mothers' milk and via the placenta. This was presented at one of the Sun Valley symposia held by the Utah group. The primary animals were mice, but a pregnant cat and a

TABLE 8.3. Effects of ^{239}Pu in Mice

Group	Dosage ($\mu\text{c}/\text{kg}$)	Survival	Hemo- globin	White Blood Cells	Liver Degener- ation	Nuclear Inclusions in Hepatic Cells	Osteogenic Sarcomas
1	40.6	+	+	+	+	+	-
2	26.5	+	+	+	+	0	-
3	15.6	+	+	+	+	+	+
4	6.1	+	0	+	+	0	+
5	3.1	+	0	+	+	+	+
6	1.7	?	0	+	+	0	+
7	0.69	?	0	0	+	0	+
8	0.34	0	0	0	0	0	+
9	0.16	0	0	0	0	0	+
10	0.08	0	0	0	0	0	0
11	0.04	0	0	0	0	0	0

Source: Reset from Finkel and Biskis 1962, p. 577. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1962.

milk goat also participated. The nuances of the experiments are wide. Some animals received their plutonium by the placenta only; some by both placenta and milk; some by milk only. Some of the rats received goat's milk containing plutonium, others received plutonium-citrate by stomach tube. The results (Finkel and Kisieleski 1976) indicate that a relatively low percentage of the plutonium entering the animal is incorporated, e.g., 0.019% in rats, 0.11% in mice, and about 0.28% in cats. Yet, because the plutonium so acquired "was avidly retained in bone" (p. 57), a significant quantity can be accumulated. For reasons that are not clear, considerably more was incorporated when it came from plutonium-milk rather than plutonium-citrate. One of the cats developed two osteogenic sarcomas 7.5 yr after ingestion of ^{239}Pu in milk. These were considered to be radiogenic. No deleterious effects were found in the several hundred mice receiving prenatal and/or neonatal exposure.

4. Comment

There were scattered other studies at Argonne that could be considered extensions of the war work, e.g., late effects of cesium in mice, plutonium metal implants, kinetics of bone seekers in dogs, etc. Most of these tie more closely to work done as a result of the fallout problems. They will be reviewed subsequently.

B. University of California at Berkeley

1. Extensions of Research on Fission Products and Heavy Metals

In the immediate postwar period, despite the changes in personnel mentioned in chapter 6, Hamilton and his staff continued tracer studies with fission

products by going on to the less abundantly produced elements. Durbin relates that this process was known affectionately among the staff as "chewing our way through the periodic table" (Durbin 1976), remarking that next to the 60-in. cyclotron the periodic table held the greatest fascination for Joe Hamilton. By 1959-1960 most of the radioisotopes from fission and many others of interest had been studied. Attention turned to problems there had not been time to attack during the war years. This resulted in the following:

a. Laboratory Report on Localization of Cerium-144

A University of California Radiation Laboratory (UCRL) report was issued on localization of ^{144}Ce in the skeletal tissues of fetal rats (Asling et al. 1957) with special concern for the site of microscopic localization. Initial binding appears to be in the organic matrix.

b. Study of the Distribution of Radioisotopes of Some Heavy Metals

This was comprehensive study of the distribution of radioisotopes of some heavy metals in the rat in which the cyclotron-produced isotopes were used strictly as tracers for learning the fate of small quantities of commonly known as well as lesser-studied (at that time) heavy metals (Durbin, Scott, and Hamilton 1957). Included were cadmium, mercury, iridium, thallium, tin, lead, niobium, tantalum, molybdenum, tungsten, technetium, rhenium, ruthenium, osmium, rhodium, palladium, and platinum. These were administered either carrier-free or at high specific activity by intravenous or intramuscular injection, or occasionally by gavage. Organs of primary deposition were cited along with total retention, organ retention, and the associated biological loss constants. There is also a brief review of the toxicological literature for each element in this very useful series.

On the basis of the distribution, absorption, and excretion, the authors divide these eighteen heavy metals into four groups:

1. those absorbed readily from the gastrointestinal tract with marked and prolonged retention in liver and kidney (cadmium and mercury in valence state +2)
2. those absorbed relatively slowly, retained transiently in liver and kidney, but for prolonged periods in skeleton (iridium, tin, lead, niobium, and tantalum in valence states +2 to +4 and without complexing agents)
3. those excreted promptly and nearly completely in urine (molybdenum, tungsten, technetium, rhenium, osmium, and ruthenium administered as complex ions)
4. those showing fairly rapid and nearly complete excretion in both urine and feces with some transient retention in kidney, spleen, and liver (rhodium, iridium, palladium, platinum in valence states +2 to +4).

This work is an important indication of how the general approaches and techniques of the Manhattan Engineer District (MED) can be expanded and benefit a much larger area of toxicology and biochemistry.

c. Work on Metabolism of Strontium-90 in Monkeys

This work was begun as a natural extension of the tracer work on radiostrontium done during the war. There was much talk of repeating the rodent work with longer-lived species (and after the fallout problems arose of extending it to long-term effects). Durbin and her colleagues, with help and encouragement

from Joe Hamilton, decided to see if metabolism of radiostrontium in primates resembled that seen in rodents and in the early dog studies. The first reports concerned the rhesus monkey, a most heroic choice of subject for metabolism studies requiring quantitative collection of excreta, if possible.^(a)

An early report was given at a Department of Defense symposium on the shorter-term biological hazards of a fallout field (Durbin et al. 1956c, 1957). Even though the paper is labeled "Preliminary," it gives a full picture of what was under way, as indicated by the abstract reproduced below:

Adult rhesus monkeys eliminated 56% of administered Sr^{90} , compared with 28% of Ca^{45} , in the urine during the first 10 days after intravenous administration.

The Sr^{90} concentration in the vertebrae was found to be reasonably representative of the skeleton as a whole in two animals whose skeletal distribution of Sr^{90} was studied. Successive amputation of caudal vertebrae is therefore recommended as the simplest and safest method of acquiring information on long-term skeletal retention of Sr^{90} in valuable animals with long life spans.

Average half times for skeletal retention of Sr^{90} were calculated for an adult male, 470 days, and for an adult female that had experienced three closely spaced pregnancies, 315 days.

Half times for skeletal retention of Sr^{90} of 155 and 195 days were calculated for the first 10 months of life of two offspring born to an injected mother.

One infant monkey retained an average of 18% of Sr^{90} administered daily by mouth for 13 weeks, whereas six adolescents retained on the average less than 5% of a daily dose during the same period of time.

A measurable amount of Sr^{90} , 23.5 dpm/g bone ash, was found in the skeleton of an uninjected control animal.

Placental transfer from a mother with a fairly well-fixed skeletal burden of Sr^{90} amounted to about 3% of the Sr^{90} content of the mother's skeleton at term.

The Sr^{90} concentration in milk samples from an injected female taken shortly after the birth of her second offspring (402 days post-injection) was three to four times the Sr^{90} level of a plasma sample taken a few days later.

(Durbin et al. 1956c, p. 173)

While the abstract does not state it, the answer to the basic question was that the metabolism of ^{90}Sr in the monkey followed qualitatively the pattern seen in other species. The biological half-time is longer than in the early rat experiments (about 400 days instead of >200 days), but not greatly different from more recent double-labeling work the authors did with ^{90}Sr and ^{45}Ca in rats (i.e., 350 days in the rats versus 400 days in the monkey). Calculation of half-time in man on the basis of relative life expectancy did not agree with the then-accepted value used by the ICRP. Longer-term studies were needed.

The retention equation was taken up further in a "Work in Progress" report by Durbin et al. in *Radiology* (1959) and a paper at the Second International Conference on the Peaceful Uses of Atomic Energy (Durbin and Jones 1958). In both instances, and in both rat and monkey, exponential rather than power functions fitted the data best. (Compare the Argonne National Laboratory studies above.) The turnover equations of rat and monkey were sufficiently alike to suggest that the information from the monkey may provide a reasonable

(a) Anyone not familiar with the pernicious excretory habits of this species should visit the nearest zoo and return with admiration for the laboratory workers who devote years to research with them. At Berkeley, liaison must have been good, for the reports identify the animals by name.

estimate for the human skeleton. However, the times are still relatively short (eight months in rat and four years in monkey). Hence, continued observation was considered necessary. This was done by addition of new monkeys and observations over a significant portion of this species' thirty-year life span. Some of the results were presented at the third International Radiation Protection Association (IRPA) Congress (Durbin et al. 1973). They will not be dwelt upon here except to say that the monkey still looked like a reasonable model for alkaline earth metabolism over long periods. This research and further new work at Berkeley with other species are more appropriately a part of chapter 13 (research stimulated by the problems of fallout) than a continuation of the World-War-II studies, although such separation is obviously somewhat arbitrary.

2. Systematic Study of the Lanthanides

In view of the important similarities and differences seen in general behavior of the lanthanides compared to the actinides, it is not surprising that the postwar extension of the work at Berkeley in biology and medicine included systematic study of both. We will examine the actinide research in a later section but give a capsule summary of the lanthanide (lanthanon) rare earth group research here.

For this work, the lanthanons were considered to fall between barium (atomic number 56) and hafnium (atomic number 72) (i.e., lanthanum through lutetium). Durbin et al. (1955) present in a UCRL report an informative capsule history of the lanthanide group, development of separations techniques, and the *raison d'être* and technical details for the extensive study carried out in the early postwar years. Many of the heavier elements not studied in the war work were added. The isotopes used were ^{140}La , ^{144}Ce , ^{143}Pr , ^{147}Pm , ^{153}Sm , $^{152,154}\text{Eu}$, ^{159}Gd , ^{160}Tb , ^{166}Dy , ^{166}Ho , ^{169}Er , ^{170}Tm , ^{175}Yb , and ^{177}Lu . Many were prepared as very pure stable isotopes by Frank Spedding's group at the Iowa State University and irradiated in the new high-neutron flux reactor at Idaho Falls to produce radioisotopes of high specific activity. Others came from the Oak Ridge Reactor or from Drs. Seaborg and Thompson at Berkeley. Thus, we see a marked departure from using almost exclusively the products of the 60-in. cyclotron at the Crocker Laboratory.

The results and technical details, but without some of the historical perspective, are in a published paper by the same authors (Durbin et al. 1956d).

The work corrected many of the defects of the war work, which had variable amounts of carrier present, sometimes quite low specific activities, and less than rigid control of age, sex, and strain of the animals. Also, the size of the experimental groups could be increased to increase statistical validity.

The earlier work used chlorides or nitrates of the elements concerned, and absorption was frequently poor. For the new work, the more soluble citrate complexes were employed. The intramuscular route of injection was used, aiming to avoid formation of insoluble radiocolloids frequently seen after intravenous injection. The oral route was used for some experiments.

Absorption from the intramuscular site was fairly complete, with the exception of a few instances involving the larger quantities injected. Absorption from the gut was quite low.

The skeleton was the most important long-term deposition site for all members of the group, and it appeared that combination was largely with organic matrix (i.e., bone protein) rather than bone mineral, thus expanding the autoradiographic findings of the war. Microscopically, the deposition in bone was largely on endosteal and periosteal surfaces and near small blood vessels in compact

bone. There were progressive increases in skeletal deposition with progression from lighter to heavier elements. Liver accumulates the lighter lanthanons as the primary deposition site, while it is only a secondary repository for the heavier members of the group.

The relative deposition in liver and skeleton is shown in figure 8.7A and B for selected members of the series.

There is a clear progression in behavior from the lighter to the heavier elements. Obviously, much of the skeletal content at longer times is due to its avid retention compared to liver. Other soft tissues accumulated less and lost it more rapidly still.

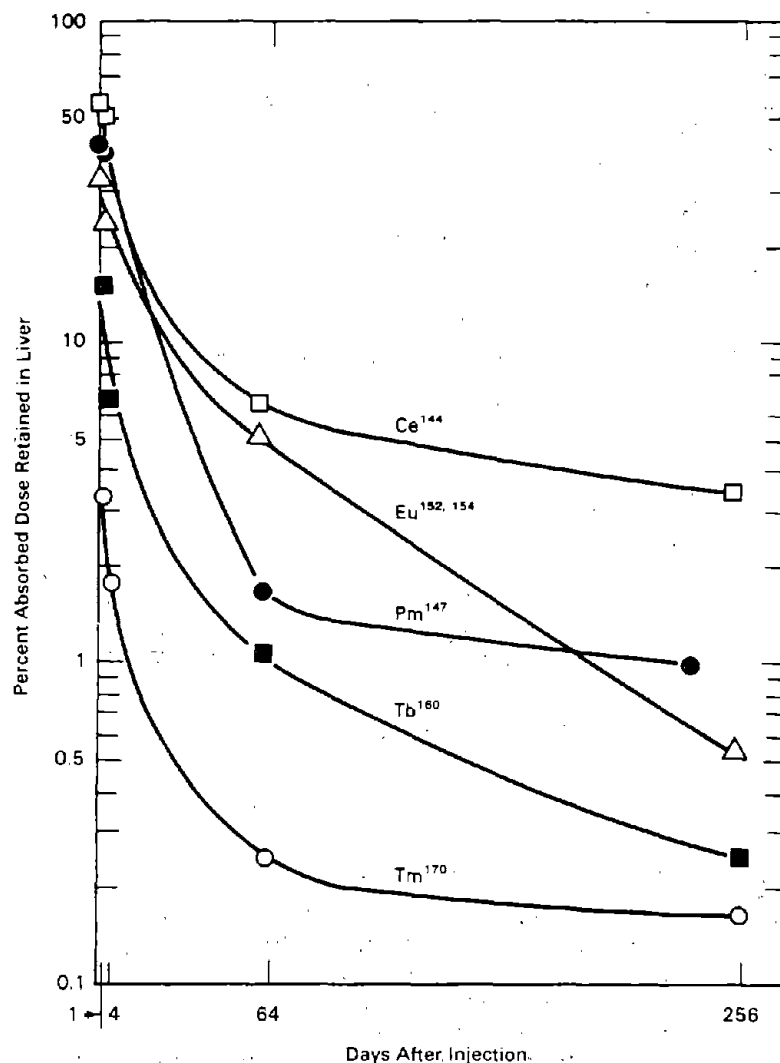


FIGURE 8.7A. Retention of several radionuclides in liver: (Redrawn from Durbin et al. 1956a.)

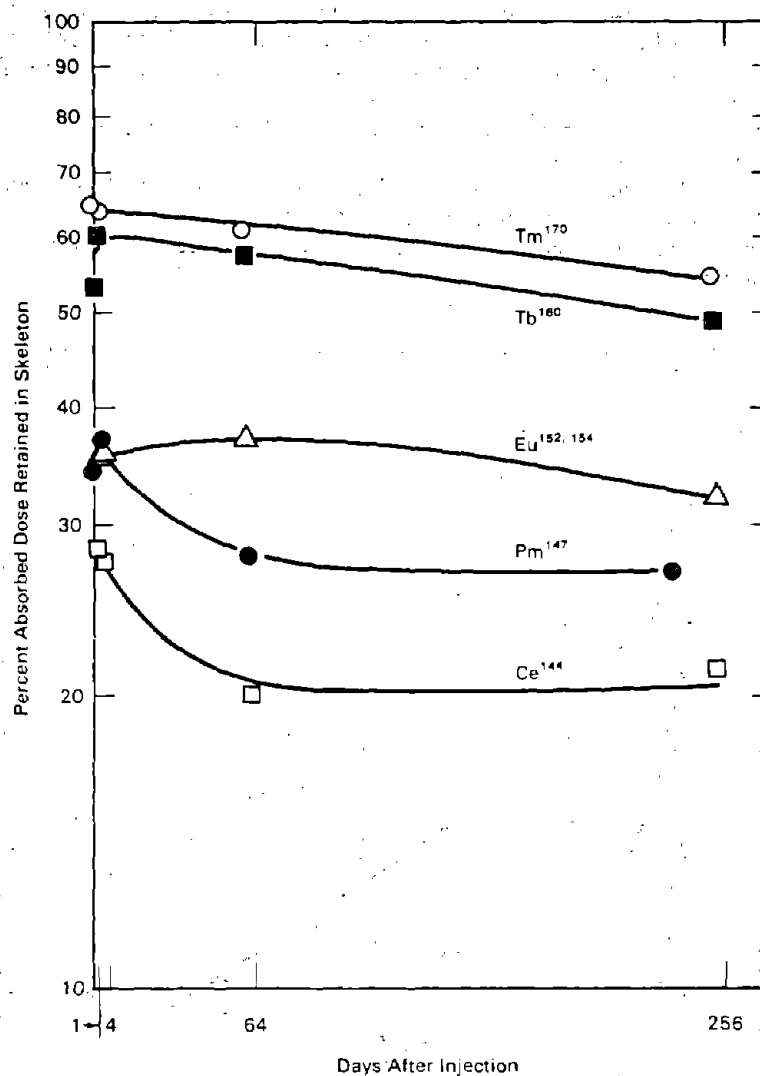


FIGURE 8.7B. Retention of several radionuclides in skeleton. (Redrawn from Durbin et al. 1956a.)

Excretion is also a function of place of the element in the series. Two routes participate: kidney to urine and liver to gastrointestinal tract via bile. The lighter elements are lost rapidly in feces by mobilization from the liver, while the heavier elements are excreted largely by kidney, at least initially. The UCRL report (1956b) and paper (1956a) by Durbin et al. give the specifics.

In a paper prepared for the landmark conference on rare earths in biochemical and biomedical research held at the Oak Ridge Institute in October 1955, Durbin et al. (1956a) presented time studies of the tissue distribution of the lanthanons given by intravenous injection. Cesium-144, $^{152,154}Eu$, ^{160}Tb , and ^{170}Tm

were employed as citrate complexes. The primary thrust of this work was, in addition to the distribution pattern, the mode of transport of microgram amounts of the lanthanons in the blood stream. This bore especially on the role of radiocolloids and aggregates, a problem of much interest to researchers with radioisotopes at that time (and seemingly somewhat neglected in present-day work). This paper, as well as the entire conference, is replete with important information and correlations on the rare earths in biology and medicine.

Interestingly, the tissue and excretion kinetics in this intravenous work were quite similar to those seen in the earlier work using intramuscular injection, something of a negation of the concerns that led to the original choice against intravenous injection.

An overview of this extensive work is provided by Durbin et al. (1955) by using much the same classification as the chemists, i.e., light, transition, and heavy lanthanons. The key findings are quoted below as an excerpt from report UCRL-3066.

1. The light lanthanons (lanthanum through samarium). Deposition was primarily in the liver and skeleton, 50% and 25% of the administered dose respectively. Elimination from the liver (presumably by way of the bile duct to the gastrointestinal tract) was quite rapid with a half time of about 15 days. Two months after injection the skeleton retained about two-thirds of its initial deposition; there was no further elimination from the skeleton during the subsequent eight months.
2. The transition lanthanons (europium and gadolinium). Deposition was more nearly equal in liver and skeleton, 30% and 40% of the administered dose respectively. Excretion was both fecal and urinary.
3. The heavy lanthanons (terbium through lutetium). Deposition was mainly skeletal, 55% to 65% of the administered dose. Elimination from the skeleton was slow with a half time of approximately 2.5 years. Excretion of extraskelatal heavy lanthanon occurred within the first two weeks after injection and was almost entirely urinary. (Durbin et al. 1955)

Before leaving the rare earth group, a few comments on the motivation for this large effort are in order:

1. The group presents an orderly progression of chemical properties based upon electronic structure. Their chemistry and methods for isolation have presented many challenges, now made less challenging by the advent of ion-exchange resins. Exploration of their behavior in biological systems posed problems of significance to understanding of which chemical properties are most important to metabolism of these elements.
2. The prevailing valence state is +3, somewhat in contrast to many of the elements in other groups of significance to internal emitter toxicology.
3. There are a large number of rare earth elements, and many occur naturally in living organisms.
4. A few rare earths assumed considerable importance in atomic energy development.
5. Many rare earths are represented in the products of nuclear fission and may be environmental contaminants.
6. Some rare earths have properties of localization in particular areas of bone and appropriate radiation energies and half-lives to be candidates for

therapeutic uses. (For example, radiogallium, a close relative of the rare earths, was studied extensively at the Oak Ridge Institute for Nuclear Studies, as we shall see in chapter 20.)

3. Iodine and Related Elements

Major background for the war work at Berkeley was, as described earlier, prewar work with radioiodine. During the war, iodine was studied as one of the fission products, and its significance to the organism was immediately appreciated. In the postwar years we are now examining, a veritable deluge of studies came from Berkeley on iodine, particularly comparisons between iodine and astatine, an alpha emitter that seeks thyroid tissue. This involved much more than the metabolic researches we have been looking at. It is part of the history of nuclear medicine, part of the history of the fallout-stimulated researches. It is considered, somewhat arbitrarily perhaps, that the story of iodine and its relatives can be treated in a more connected way using a different format, where several lines of investigation can be viewed simultaneously. Thus, the Berkeley work in this field will be reserved for chapters 10 and 13 and, to a lesser extent, chapter 20.

4. Actinide Research in the Postwar Years

The Berkeley group did relatively little postwar actinide research that can be tied as closely to the war work as the experimental studies on lanthanons and alkaline earths just described, or the large effort with iodine and astatine to be described later. But there were very significant contributions. Some were additional laboratory experiments, particularly with the transplutonics. Others were enormously useful general reviews and syntheses of information from many sources. We will look first at some of the new experimental work.

In the international symposium, *Delayed Effects of Bone-Seeking Radio-nuclides*, a festschrift celebrating the fifteenth anniversary of the Utah Project, held in Sun Valley, Idaho, in September 1967, Durbin, Jeung, and Williams (1969) presented data on the behavior of ^{241}Am and ^{45}Ca in the skeleton of Charles River rats. Contrast of the retention curves, which were sums of exponentials, occurred between different bones and between the radioelements. The authors identify the segments with physiological processes, identified by autoradiographic, tracer, and histologic means. The loss curves for americium had fewer components than those of calcium, and there were indications that it did not participate in exchange reactions in bone, in contrast to the alkaline earths and alkali metals. It was retained indefinitely in bones like rib and mandible, which do not experience net mineral loss in old age. In addition, redistribution could be correlated with specific processes in bone. As a supplement to the life-span tracer studies, a background of growth and senescence in the female rat was provided. The animals showed no radiation-connected pathology at the levels used. A kinetic model of americium metabolism was derived for the rodent.

Further studies were seen primarily in papers presented at meetings, e.g., Durbin, Williams, and Jeung (1961, 1972). Each concerned primarily elaboration of metabolism and mechanisms and used the monkey, the cynomolgus monkey in the latter work—a more tractable beast than the rhesus monkey. In addition to these, there were several unpublished (e.g., Durbin, Jeung, and Williams [1972b]) studies that came to light in Durbin's monumental review of the transplutonium elements to be discussed presently.

A somewhat generalized study using examples of each major group of bone-seeking elements, including plutonium and americium, was published by Asling et al. in 1952. This was an autoradiographic study of the deposition and behavior of several elements in the costochondral junction in the bones of rats, a site that contains periosteal tissue with osteogenic potential, yet not immediately adjacent to bone. The elements used were calcium, strontium, promethium, plutonium, and americium, all in high specific activity. Details of localization are given, and they confirmed, in general, ideas from earlier work.

The second aspect of the Berkeley postwar work with the actinides consisted of a series of enormously useful, scholarly, and sophisticated correlative reviews. These are pertinent to all aspects of the ongoing biomedical research with the actinides and will be considered as we review the specific subjects. But we should see them once all together. Therefore, they are listed below with a few comments on what they contain:

1. Metabolic Characteristics within a Chemical Family. P. W. Durbin, *Health Phys.* 2:225-238 (1960). A broad review of seventy elements: alkali metals, alkaline earths, lanthanides, and actinides; Groups IV, V, VI, VII, and the platinum metals. Properties that determine biological behavior are reviewed.
2. Distribution of the Transuranic Elements in Mammals. P. W. Durbin, *Health Phys.* 8:665-671 (1962). A review of chemical properties of both actinides and lanthanides and comparisons of their biological behavior.
3. Plutonium in Man: A Twenty-Five Year Review. P. W. Durbin, Report UCRL-20850 (June 1971). A reanalysis of the data from the injected patients described in chapter 7.
4. Plutonium in Man: A New Look at the Old Data. P. W. Durbin, chapter in *Radiobiology of Plutonium*, B. J. Stover and W. S. S. Jee, eds. J. W. Press, Salt Lake City (1972). Also report UCRL-20850 (no date). A retrospective study primarily of the patients described in chapter 7 in light of the new knowledge.
5. Plutonium Deposition Kinetics in the Rat. P. W. Durbin, M. W. Horovitz, and E. R. Close, *Health Phys.* 22:731-741 (1972). Development of a kinetic model and its implications for mechanisms.
6. Metabolism and Biological Effects of the Transplutonium Elements. P. W. Durbin, chapter 18 in *Handbook of Experimental Pharmacology*, Vol. 36, Hodge, Stannard, and Hursh, eds. Springer-Verlag, pp. 739-896 (1973). A comprehensive compilation and analysis of all of the biomedical data on transplutonics, which had hitherto been scattered throughout the world literature. In itself, it is worth the rather heavy price of the book for anyone really needing to know.
7. Behavior of Plutonium in Animals and Man. P. W. Durbin, Plutonium Information Meeting for an ad hoc subcommittee of the Advisory Committee on Reactor Safeguards, Los Alamos, New Mexico (January 1974a). A comprehensive review.
8. Transfer of Plutonium from Soil to Plants: A Review of the Problem. P. W. Durbin, Report UCID-3689 (September 1974b).
9. Plutonium in Mammals: Influence of Plutonium Chemistry, Route of Administration and Physiological Status of the Animal on Initial Distribution and Long-Term Metabolism. P. W. Durbin, *Health Phys.* 29:495-510 (1975). Current concepts of plutonium metabolism reviewed.

10. Survival, Causes of Death and Estimated Tissue Doses in a Group of Human Beings Injected with Plutonium. R. E. Rowland and P. W. Durbin. In *Health Effects of Plutonium and Radium*, W. S. S. Jee, ed. J. W. Press, Salt Lake City, pp. 329-341 (1976). Adds dose calculation to the review of the plutonium patients.
11. A Summary of Actinide Biological Research, 1943-1977. P. W. Durbin. Workshop on Research Needs in Actinide Biology. DOE Conference-770491 (1978b). Appendix A (1978b). A wide ranging history; Appendix B, Actinide Biological Research in Progress (1976-1977), (Durbin 1978a). A review for purposes of evaluating all programs.

5. Radium-223, The Daughter of Actinium

The interest in actinides at Berkeley included tracer-level metabolic research with ^{227}Ac (Hamilton 1954, p. 23) and, for the first time, an effects study using a daughter product, ^{223}Ra . This isotope is an alpha emitter of 11.2-days half-life and has a series of short-lived alpha-particle descendants with energy totaling 20 MeV, plus two beta emitters with an average energy of 0.5 MeV each. It was given intramuscularly as a citrate complex (Hamilton 1954, p. 26; Durbin et al. 1958).

Radium-223 proved to be highly toxic acutely, quite in contrast to the longer-lived radium isotopes, which are surprisingly ineffective acutely. The mean lethal dose in thirty days was about $0.05 \mu\text{Ci/g}$ body weight, compared to about $1.6 \mu\text{Ci/g}$ for ^{226}Ra in adult rats. A full account is given of hematological effects and gross as well as some microscopic pathology. The possible reasons for the difference in acute toxicity between ^{223}Ra and ^{226}Ra are given. Obviously, the initial dose rate with ^{223}Ra is much higher than with ^{226}Ra . But, in general, dose-rate influences are small with alpha emitters and when present seem more to favor increased effectiveness of protracted doses. Differences in the blood-forming centers were marked, e.g., very little ectopic myelopoiesis in the ^{223}Ra animals, while with other radium isotopes there were many centers of blood-cell regeneration, which might tide the animals over the acute radiation syndrome phases.

This interesting work, while quite complete in the UCRL reports, seems never to have been published in the open literature.

6. Crocker, Donner, and the University of California, Berkeley Radiation Laboratory

The internal emitter metabolism and toxicology work became part of the Donner Laboratory (or so the by-lines in the publications stated for a while after the transition). Donner had a long history of interest in radioisotopes, as tracers (Jones et al.), in nuclear medicine (John Lawrence et al.), and superb work with the variety of high-energy sources available in the Radiation Laboratory (Tobias et al.) "on the hill." In due course, the internal emitter toxicology research was moved to a laboratory building also on the hill behind the Berkeley campus in the University of California, Berkeley Radiation Laboratory area. While no longer identified as a separate enterprise by the appellation "Crocker Laboratory," the group continued to have a fair degree of autonomy. Also, the new location provided more adequate facilities for care of animals.

Besides their inherent value and their usefulness to the plutonium Project workers and their successors, the metabolic behavior data from

these postwar studies, as well as the earlier data, were fed directly into the work of Committees II of the ICRP and the National Council on Radiological Protection and Measurements (NCRP), as we shall see in chapter 16. And it is all part of the foundations of nuclear medicine—which was where the interest began in the first place in the late 1930s.

III. New Projects: The King-Sized Experiments

A. Background

“One thing that cannot be bought in biological research is time.” John R. Totter, chairman of the AEC’s Division of Biology and Medicine, made this remark toward the latter part of the AEC years at the twentieth anniversary celebration of the University of Utah Laboratory of Radiobiology (Totter 1972). The reader must already have become aware of that axiom for internal emitter research in the chapter on radium. We have felt the problems, perhaps subliminally, in our reviews of work with rodents that seemed to die of pneumonia, or the diseases of aging, at just about the time the changes of most interest, such as cancer, might have turned up at relatively low levels of exposure. We saw in chapter 2 that it took eleven years in a single experiment to establish some of the really long-term effects of inhaled uranium.

Many attempts have been made recently to speed up the process by use of cells in tissue culture or other surrogates for the long-term effects. But in 1947 these were unknown—and even now we are not sure we have a reliable substitute. Today the field of chemical toxicology is faced with learning about the long-term effects of thousands of chemicals. Whether or not they can find a way to cut some corners in time, it is essential that all interested in chemical toxicology take a lead from the enormous efforts put into radiation toxicology.

There was a mass movement in the early days of the AEC toward setting up experiments with long-lived animals in sufficient numbers to do each job as an entity and to avoid expensive repetitions. This was true of both the problems of external radiation and of deposited radioisotopes. They included eventually the Argonne National Laboratory and the Hanford works of General Electric as well as the Universities of California, Michigan, Rochester, Utah, and Wisconsin. At Oak Ridge, the “megamouse” experiment was set up for study of genetic effects of radiation, and it is still going at well past several million mice. (Obviously, genetic work of the type needed could be done only with a short-lived species. But this was one of the few exceptions to the trend toward larger, longer-lived animals). The Department of Health, Education and Welfare joined the procession by sponsoring a large experiment using external radiation with dogs at Colorado State University.

The granddaddy of them all, at least for internal emitter research, and in some respects the most uniquely organized, was the project at the University of Utah at Salt Lake City. We will examine its genesis and accomplishments in some detail in the following section.

B. The University of Utah Beagle Project

1. Origin

This project had its origin at Los Alamos. The memory of what went on at the Chalk River Tri-Partite Conference on Permissible Doses lingered in the minds

of people like Wright Langham, whom we met in chapter 7, and of Tom Shipman, the Health Division leader at Los Alamos. Work with plutonium and radium in mice had led to tentative adoption of a new plutonium standard that would have shut down Los Alamos.^(a) Yet, all concerned knew that extrapolation to man from the work with rodents had many problems. The year 1950 saw these problems lead to the organization of an entirely new and very large project.

First let us look at the setting as seen in an extract from a letter from Thomas L. Shipman, M.D. to Dr. Shields Warren, director of the Division of Biology and Medicine of AEC, dated June 19, 1950:

At the conference on tolerances which was held at Chalk River in October of last year, it turned out that tolerance figures for plutonium were decided principally on the basis of some work which Austin Brues had done using several hundred rats and mice and six dogs. The work which Dr. Brues did was excellent, and we have no desire to cast any doubts on what he has done. I am certain that he will agree, however, that the situation produced a decision of rather far reaching consequences which was based on a foundation that was shaky simply because there was not enough experimental evidence.

Rats and mice are excellent animals to use for certain purposes, but all of us are aware that in studies with radium, plutonium and other bone-seekers, they have certain very definite disadvantages. In the first place, the long bones of the rodent do not unite at maturity and they just continue to keep growing until they die. Furthermore, these animals have a distressing way of dying of pneumonia at just about the time they are ready to develop bone tumors, pathological fractures, and other evidences of damage from the material under study. This has required that they be given rather massive doses of plutonium or whatnot, if significant effects are to be observed. As should be obvious, we are no longer much interested in the effects of massive doses; we must concern ourselves with the long-term effects of doses in the vicinity of the tolerance level. The dogs that Dr. Brues used, six of them, were, as I understand it, the survivors from an experiment to determine lethal doses. They too had received doses far in excess of the range in which we are interested.

To cast even more doubt on the validity of our existing data, is the current indecision as to the actual toxicity of radium itself. It was assumed that this matter was pretty well nailed down, but recent information about mesothorium has found the subject pretty much up in the air. We have little choice but to go back and start at the beginning. Here again the use of animals larger than rodents is essential; rodents excrete about 85% of their radon; while man excretes 40-50%. Dogs should resemble man far more closely in this respect, as well as having a skeletal weight which in proportion to total body weight would far more closely approximate man.

Further along, Dr. Shipman emphasizes the keen interest of the Los Alamos people in getting the new project started. But it soon became apparent that Los Alamos was not a very suitable site for such an operation. Los Alamos was still a very restricted area and a very expensive place to operate. The plan was for about two hundred dogs to receive plutonium and radium by injection and by inhalation in a separate experiment.

Almost immediately, Austin Brues was brought into the discussion. After all, he had supplied the original data (along with his colleagues such as Miriam Finkel, as we have already seen in chapters 6 and 7, and earlier sections of this

(a) The reasons it did not are reviewed in chapter 16.

chapter). And since there were strong reasons to include ^{226}Ra , Robley Evans was soon invited and became an enthusiastic participant.^(a)

Shields Warren, the director of the new AEC Division of Biology and Medicine, was not hard to convince of the need for such an experiment. That year records many letters, as well as several meetings, between him and the principals. Wright Langham took the major initiative for following through and presenting the plans in greater and greater detail to potential sponsors as the project took shape.

But it was a project without a home, indeed without a director or personnel. It had only Langham, Brues, Evans, and, to a lesser extent, Shipman and Shields Warren to urge that it be done and help it in every possible way. But when people with that much interest and clout get excited about a new enterprise, something is likely to happen. And it did. John Z. Bowers, who had been in the AEC Division of Biology and Medicine, accepted the post of Dean of the Medical School at the University of Utah and agreed to see if the project could be placed there. The advantages of being on a university campus, and part of a medical school, were stressed for their importance in obtaining consultative assistance and in providing a home for the new personnel. Bowers persuaded some key department heads in the school that it was a good idea, and the project acquired a home.

The details of assembling space, facilities, and personnel are told partly in some of the volumes commemorating the several anniversaries of the project, most completely in the paper by Betsy and Clarence Stover in the twentieth anniversary volume (Stover and Stover 1972). But the full story can be gleaned only from the correspondence, minutes of meetings, and personal reminiscences of those concerned. Many of the original personnel are still available to help anyone interested in further specific details.

2. The Next Steps

Langham, Brues, and Evans—who were later to be part of the group called “The Founding Fathers” of the Utah Project—got right to work on detailed plans for the experiments. The dog was the instant and unanimous choice. Early it was thought that the American foxhound would be a good choice, but it soon became evident that adequate supplies of this animal would be a problem. Meanwhile, in other quarters, the advantages of the beagle had stimulated interest, and their similarities to man in the areas of most interest to the project cast the die.

A history of the beagle strain and of its adaptation to research was given by Rehfeld, Blomquist, and Taylor (1972), also at the twentieth anniversary meeting. Among the advantages were the unusual uniformity present in the breed, made even greater by the fact that a breeding colony was to be established; equality in stamina; adaptability (as a pack dog) to living in a colony; a relatively docile, if occasionally stubborn, disposition;^(b) and easy liaison with humans.

(a) The problems of the radium standard occasioned by the realization of the special toxicity of mesothorium are probably somewhat exaggerated in the Shipman letter quoted. As we saw in chapter 1, they did as much to help explain some anomalous results in the human as to raise questions about the validity of the standard. But there was no question that ^{226}Ra had to be the bench mark in such an experiment.

(b) This was usually an advantage in the highly routine existence of the research colony, but not so helpful when a change in routine was attempted.

Since the details are important not only to our review of the development of the Utah project, but to many of the other postwar experiments, two excerpts from the pertinent papers are given below. The first is the abstract of the Rehfeld, Blomquist, and Taylor (1972) paper at the twentieth anniversary symposium:

Throughout its history of at least 500 years the beagle has been fostered and developed as a small, hound-type hunting companion, primarily in France and the British Isles. Americans started importing beagles from the British Isles in the 1870's and since that time the breed has steadily grown in popularity as a hunting, companion, and research dog. Its history as a research animal extends back only to the comparatively recent year of 1950. Starting at that time, the Radiobiology Division at the University of Utah has had a major role in pioneering the in-laboratory breeding and care of beagles for research. This laboratory has produced 1427 beagles since 1950 with a total of 32 animals acquired for breeding purposes; each of the 103 of the laboratory-bred animals produced one or more young to contribute to this total. The descendants of 18 acquired and 21 laboratory-bred animals were favored in selection of successive generations of breeding stock. All of the 21 dogs were related to the original 18, so a large proportion of the colony dogs are directly related to them. Although a large number of the laboratory-bred beagles are inbred, in a majority (80.3%) of these, the inbreeding is less than that which would result from one sibling mating. This colony of beagles was started in 1950 at a time when there were no large research dog colonies in existence and soon became a model colony within a prototype physical facility. (Rehfeld, Blomquist, and Taylor 1972, p. 47)(a)

The second is a list of scientific advantages from a paper by Mays et al.: "Advantages of the Beagle in Long-Term Radiobiological Studies" (1973, p. 110):

1. Skeletal similarity to man.
2. Importance of jaw syndrome induced in man and beagles, but not rodents.
3. Relevant radiographic information.
4. Osteosarcoma location.
5. Possible differences in shape of dose-response: Rodents vs. large mammals.
6. Unique sex difference in bone sarcoma induction: Mice vs. humans and beagles.
7. Growth dynamics of osteosarcomas.
8. Liver retention of ^{239}Pu .
9. Advantage in obtaining sequential blood samples in beagles.
10. Corticosteroid production similarity between man and beagle.
11. Transaminase and alkaline phosphatase similarities between man and beagle.
12. Advantage of larger organ size in radionuclide distribution studies.

Bustad and colleagues also extolled the virtues of the beagle (and he was a pig man!) in another paper at the twentieth anniversary symposium (Bustad et al. 1972).

Not mentioned in these summaries is the fact that this breed has a very low normal incidence of bone tumors, i.e., osteogenic sarcomas, and of most of the other clinical entities of importance to internal emitter toxicology.

The "Founding Fathers" also occupied themselves with questions of what elements to use, what doses to employ, and what route of entry. Plutonium-239 and ^{226}Ra were the original elements at issue. Robley Evans soon convinced

(a) Not mentioned is a large colony at Cornell University developed mainly for other types of work. The colony at the University of California, Davis, was developed shortly after these.

everyone that the radium data could not be useful for comparison to man unless the toxicity of mesothorium was known in the dog. Thus, mesothorium (^{228}Ra) and radiothorium (^{228}Th), the alpha-emitting decay product of ^{228}Ra , entered the plan. The elements were to be as nearly pure as possible.

There was much debate over dosage levels. A pure arithmetic progression seemed unlikely to cover the range without having to use too many levels. A geometric progression might place too much emphasis on the low levels where little was expected to happen. (This was actually incorrect. Effects occurred at even the lowest levels of plutonium, and new, still lower levels had to be introduced later.) The progression adopted resembled one suggested by George Sacher at Argonne: 1:9:40:83:175, thus giving larger ratios at the lower levels where uncertainty was the greatest.

The anchor points were to have level 1 equivalent to 10 times the accepted maximum permissible level for radium, equivalent to $0.1\ \mu\text{Ci } ^{226}\text{Ra}$, and the maximum at 1,750 times the bench mark. The doses for the other elements were determined from the best estimate of the toxicity ratio from the work described in chapters 6 and 7.

Finally, it was decided to forget about imitating field or industrial exposure situations and do an experiment with the least possible uncertainty regarding initial dose—i.e., intravenous injection of the elements complexed with citrate to avoid, if possible, problems with radiocolloids.

3. The Utah Project Gets Under Way

The first contract between the AEC and the University of Utah became effective July 1, 1950. But Dr. Bowers did not arrive until November, although some staff had already been hired (e.g., Betsy Stover, Garth Westenskow). A veterinarian, Dr. Robert C. Bay, joined the group soon after Dr. Bowers's arrival, and it was fast apparent that the only realistic course was to first establish a breeding colony to supply experimental animals.

In due course, a physicist (Marvin Van Dilla) and a bone histologist (James Arnold) arrived, followed by several veterinarians, a radiologist, hematologist, etc., either full or part-time. We will meet these people in our review of the results.

On the administrative side, Dr. Bowers handled the necessary interactions with the university, while in Washington, Dr. Warren and his special assistant, Dr. Walter Claus, saw to the financial and planning aspects from AEC's viewpoint. In a sense, these three, Bowers, Claus, and Warren were founders too, perhaps "founding uncles" or "rich uncles" rather than "Founding Fathers." Their portraits introduce the twenty-fifth anniversary volume. And there were others, like H. D. Bruner who helped at the AEC level somewhat later on, and who, we will see, had considerable influence at the Washington level on the planning for all radioisotope toxicity experiments. Also at headquarters, Dr. C. W. Shilling, Deputy Director of the Division, shouldered responsibilities for seeing the ideas implemented by Congressional appropriations.

Temporary kennel facilities gave way to the first real kennel for the breeding colony in March 1952. The first beagle to be injected received $3.05\ \mu\text{Ci } ^{239}\text{Pu/kg}$ intravenously on June 24, 1952. The project was officially launched.

4. Inhalation Aspects

In the early plans, it was proposed that a portion of the animals be exposed by inhalation since this was, of course, the likely route of entry. It was not intended

to be very extensive. The intratracheal injection route was considered seriously. But the Los Alamos people had no facilities, nor did they wish to do the necessary planning and building. Eyes turned toward Rochester as the project with the most experience with inhalation work. Harold Hodge, who had much to do with the uranium inhalation work, as we saw in chapter 2, was contacted and invited to meet with the planners. For some reason he was not free to attend, but Drs. Henry A. (Harry) Blair, director of the University of Rochester Atomic Energy Project, and William F. (Bill) Neuman, one of Hodge's right-hand men, did get out to a meeting in the desert. Although they went with little enthusiasm for a new project, the needs impressed them, and a promise of help of some sort came soon afterwards. In fact, as usual, Rochester thought they could fit it in without major additional expenses if a few month's delay were not crucial. Actually, except for some crude experiments done at Rochester and Chicago during the war with burning wires, and some important pioneering work at Berkeley, no one was really prepared to purposely put up aerosols of highly dangerous radioactive materials. Rochester had to fashion an entirely new program, as we will see in chapter 9. But the promise was made and eventuated in Newell Stannard's becoming director of the Radioactive Inhalation Section at Rochester. This episode also resulted in Harry Blair's becoming a member of the Advisory Committee for the Project, an expanded version of the "Founding Fathers."

Meanwhile, Bowers had settled in at Utah. At some time after they were well into operation, he decided that they needed an inhalation chamber there to help with inhalation studies pertinent to the uranium miner problems of the Colorado Plateau. Duncan Holaday, who was stationed in Salt Lake City, had been trying to get help, as we saw in chapter 3. John Bowers decided to try a small foray into the inhalation field and bought a chamber using some funds from a National Institute of Health grant (Stover 1980).

A few exposures were made, and some work was done with ^{233}U , but the expertise needed for successful inhalation toxicology work was apparently not present, or the group had too much else to do. The chamber was sold back to Rochester. So far as this author can ascertain, no formal reports appeared.

5. A Comment on Significance

Before continuing further, we must pause to realize what a unique phenomenon in scientific research this project represented. So far as this author knows, this was the first occurrence in peacetime of a contract between a university and a government agency for a *specific* long-term study, at least in the biological sciences. It was most unusual in having the plans essentially laid out ahead and a powerful advisory group exerting control down to details of dose levels, numbers of animals per group, numbers of controls, etc., even before the personnel had been assembled. Quite the antithesis of the conventional academic research operation! Yet it worked! The credit goes, in part, to the unusually perceptive individuals who saw the needs and realized planning must be in-depth before anything was started. There could never be a repeat. The staff was vigorous, keen, and well able to do collaborative research. This included the original staff and later joiners in the form of graduate students who finished up and joined the ranks (e.g., Jee, Mays).

But I think much credit goes also to the management and attitude of AEC's Division of Biology and Medicine. Their long-term support was essential. Yet,

they managed to achieve all primary objectives while allowing major degrees of freedom in an atmosphere of mature cooperation between partners in an important enterprise. And this was the story at other similar projects too.

An appropriate and interestingly original summary of what was done and how it was done appears in the parable-style paper entitled "Genésis" given by Walter Claus at the twenty-fifth anniversary symposium (Claus 1976). This is reproduced in its entirety as note 1 at the end of this chapter.

6. The Modus Operandi

It was obvious that the injections had to be staggered, since there was not room for all of the animals planned at any one time. The result was a sort of unit approach with groups receiving a single element and their controls starting out together. This could work because of the extraordinary uniformity of the animals and of the conditions.

Each animal was treated as a patient in a well-run hospital, even better, because the complete pedigree of each was known in some detail. There were routine operations that can be seen best in the summary of the first ten years published by Dougherty et al. (1962b). These extended from standardized procedures for preparing an animal to enter the experiment (at approximately 1.4 yr of age) through regularly scheduled clinical and x-ray examinations, to the elaborate and complete post-mortem work-ups. No one can complain that this experiment concentrated too much on cancer as an end point—which some do.

The dogs were confined to stainless steel metabolism cages for one week prior to and for three weeks after injection for the collection of urine and feces. This aided in the estimates of retention and reduced contamination of the outdoor runs. There were interim excreta collections over four-day periods throughout. In addition, in-vivo counting was done where feasible, using a modification of the Los Alamos liquid scintillation counter called "K-9," or a modification of it called "K-9, Bark II."^(a) At autopsy, tissues were analyzed radiochemically. Radon in expired air was measured in the ^{226}Ra animals and thoron in the mesothorium dogs. Thus, retention equations could be derived as a composite from several sources of information.

In table 8.4, the injected doses and numbers of dogs at the end of the first decade are shown. There were many intermediate stages, of course, in reaching this point.

The reader will note that a new isotope, ^{90}Sr , had been added, resulting, of course, from the problems generated by fallout from nuclear weapons testing. Also, some lower and intermediate dosage levels appear. These were inserted as it became apparent that the original plans needed modification to lower levels and some intermediates for certain elements. By virtue of these, the total number had gone from the earlier estimates to over four hundred dogs.

Level 1 was the bench mark, determined from ^{226}Ra by the relation:

$$\frac{10 \times 0.1 \mu\text{Ci } ^{226}\text{Ra}}{70\text{-kg Standard Man}} = \frac{0.0143 \mu\text{Ci } ^{226}\text{Ra}}{\text{kg of Dog}}$$

(a) This picturesque terminology has been attributed to Betsy Stover, the project's principal radiochemist.

or, assuming 25% retention, this becomes:

$$\frac{1}{0.25} \times \frac{0.0143 \mu\text{Ci } ^{226}\text{Ra}}{\text{kg of Dog}} = \frac{0.057 \mu\text{Ci } ^{226}\text{Ra}}{\text{kg of Dog}}$$

which would be the injected dose equivalent to ten times the maximum permissible burden in man of $0.1 \mu\text{Ci}$ of ^{226}Ra .

The other levels have the following relationships to level 1:

Level	Relation to Level 1
0.2	1/9
0.5	1/3
1.5	2x
1.7	3x
2	6x
3	18x
4	54x
5	162x

Level 1 for elements other than ^{226}Ra was based on retention factors characteristic of that element as described by Dougherty et al. (1962a,b) or as later modified.

TABLE 8.4. Injected Doses and Numbers of Dogs^(a)

Dose Level Code	Injected Doses ($\mu\text{Ci/kg}$)					Number of Dogs					
	Ra ²²⁶	Pu ²³⁹	Ra ²²⁸	Th ²²⁸	Sr ⁹⁰	Ra ²²⁶	Pu ²³⁹	Ra ²²⁸	Th ²²⁸	Sr ⁹⁰	Total
5	10	2.8	10	2.8	100	10	9	7	2	12	40
4	3.2	0.90	3.2	0.90	32	12	12	7	4	12	47
3	1.1	0.30	1.1	0.30	11	12	12	12	12	12	60
2	0.34	0.096	0.34	0.096	3.4	12	12	12	12	12	60
1.7	0.17	0.048	0.17	—	1.7	12	12	12	—	12	48
1.5	—	—	—	0.032	—	—	—	—	12	—	12
1	0.057	0.016	0.057	0.016	0.57	12	12	12	12	12	60
0.5	—	—	0.019	0.0051	—	—	—	6	12	—	18
0.2	—	—	—	0.0017	—	—	—	—	8	—	8
0	0.0000	0.0000	0.0000	0.0000	0.0000	12	12	12	12	12	60
Total						82	81	80	86	84	413

(a) Levels 1 to 5 were injected initially, 1.7 was added later, and 0.5 and 0.2 still later.

Source: Modified from Dougherty et al. 1962b. Reprinted with permission of Academic Press, Inc., Orlando, Florida, copyright 1962.

It will be noted also that there are twelve controls for each radioisotope for a total of sixty. There was a considerable polemic in the early years over how many controls there should be. A statistician named E. Brandt took part in the early planning and concluded that many fewer controls (i.e., fifteen) would be

adequate. Statistically he was correct, and it was important that space should be concentrated on experimental animals. But the advisory group was concerned. They could visualize how controls would have to follow along in time with their specific injected group and how unexpected losses to disease might reduce the number of controls dangerously. Also, much depended on knowing a lot about the untreated population. So they overrode the statistics, and on the basis of intuition as much as rigid proof made the control group larger and decided that litter mates should be distributed into isotope and control groups. This turned out to be a good plan, although strictly speaking it exceeded the numbers needed for statistical validity, if all went well.

Dr. Bowers left in 1955 to go to the University of Wisconsin as dean of the Medical School, and Dr. Thomas Dougherty took over direction of the project. It became associated with the Department of Anatomy, of which he was chairman, where it remained until Dr. Dougherty died in 1979. Graduate students like Webster Jee and Charles Mays finished their degrees and joined the group. Indeed, they became anchor men, and both, especially Jee, assumed temporary directorship after Dr. Dougherty's death. While there has been some turnover, the staff remained remarkably stable, as needed for successful prosecution of such an experiment. The data began to accumulate in enormous quantities. Yet, reports kept flowing, not only from the main experiment, but from special studies individual staff members could do as their interests dictated. We will review the results very briefly in the section to follow.

7. Results at Utah

The information from this very large project is, of course, impossible to capsule without distortion or omission of many important contributions. This is especially true of the contributions the work has made to basic biological science. Fortunately, in-house reports have been regular and complete and publications most adequate. Particularly useful are the book-sized reports of symposia held approximately each five years (e.g., Dougherty et al. 1962a and subsequent volumes). Since these have been, particularly recently, international in scope and very well organized, their contents provide not only summaries of the Utah results, but a chance to assimilate what was going on worldwide and how the Utah work fitted into the entire field. In addition, semiannual and annual reports presented regular updates of the work as well as numerous special studies.

Americium-241 was introduced in 1966, partly to have a transplutonium element in the scheme, and partly because of its importance as a decay product of ^{241}Pu . (a)

a. Bone Tumors and the Toxicity Ratio

The first dog to die as a result of an osteosarcoma was also the first animal injected at the highest level of ^{226}Ra . The date was October 1955, not much more than three years after the injection. The first osteogenic sarcoma in the plutonium group was also at the highest level. The date of euthanasia was

(a) The plutonium produced in high flux reactors contains more of the heavier isotopes of plutonium, and ^{241}Am became of importance as a potential contaminant. The Utah project, however, continued throughout with "old-fashioned" plutonium from a generous supply made available by Wright Langham.

July 1956. These early occurrences presaged the first general finding: the incidence of bone tumors would be beyond expectations in the planning. Lower dose levels would be needed. This was done as indicated earlier, with both more steps and lower levels.

The complete experiment as it existed in the twentieth year is shown in table 8.5A and B. Table 8.5A shows the doses, and table 8.5B shows the numbers of animals. Note that the controls had to be increased for ^{239}Pu and ^{226}Ra because of the new levels, bringing the total controls to 80 and the total

TABLE 8.5A. Injected Doses in $\mu\text{Ci/kg}$, Utah Project

Dose Level	^{239}Pu	^{226}Ra	$^{228}\text{Ra}^a$	^{228}Th	^{90}Sr	^{241}Am
5	2.9	10	8.5	2.7	97	2.8
4.5	—	—	—	—	64	—
4	0.91	3.2	2.6	0.86	33	0.91
3	0.30	1.1	0.97	0.29	11	0.30
2	0.095	0.34	0.31	0.092	3.5	0.096
1.7	0.048	0.17	0.15	—	1.7	0.048
1.5	—	—	—	0.030	—	—
1	0.016	0.062	0.050	0.015	0.57	0.016
0.7	0.010	—	—	—	—	—
0.5	0.0055	0.022	0.018	0.0052	—	0.0053
0.2	0.0019	0.0074	—	0.0017	—	0.0018
0.1	0.00064	—	—	—	—	—
0	0	0	0	0	0	—

^aExcludes ^{228}Ra dogs injected with more than 1% ^{228}Th contamination.

Source: Reset from Stover and Stover 1972. Reprinted with permission of J. W. Press, Salt Lake City, Utah, copyright 1972.

TABLE 8.5B. Dogs Per Dose Level, Utah Project

Dose Level	^{239}Pu	^{226}Ra	$^{228}\text{Ra}^a$	^{228}Th	^{90}Sr	^{241}Am	Total
5	9	10	4 ^b	2	12	2	39
4.5	—	—	—	—	12	—	12
4	12	12	5 ^b	4	12	12	57
3	12	12	9 ^b	12	12	12	69
2	12	12	9 ^b	12	12	12	69
1.7	13	12	10 ^c	—	12	13	60
1.5	—	—	—	12	—	—	12
1	24	22	10 ^b	12	12	13	93
0.7	11	—	—	—	—	—	11
0.5	10	10	12	12	—	14	58
0.2	10	10	—	12	—	14	46
0.1	10	—	—	—	—	—	10
0	22	22	12	12	12	—	80
Total	145	122	71	90	96	92	616

^aExcludes ^{238}Ra dogs injected with more than 1% ^{238}Th contamination.

^b1 additional dog injected with a solution in which $(\mu\text{Ci } ^{228}\text{Th}/\mu\text{Ci } ^{228}\text{Ra}) = 0.15$, and 2 additional dogs injected with a solution in which $(\mu\text{Ci } ^{228}\text{Th}/\mu\text{Ci } ^{228}\text{Ra}) = 0.03$.

^c2 additional dogs injected with a solution in which $(\mu\text{Ci } ^{228}\text{Th}/\mu\text{Ci } ^{228}\text{Ra}) = 0.03$.

Source: Reset from Stover and Stover 1972. Reprinted with permission of J. W. Press, Salt Lake City, Utah, copyright 1972.

number of animals to 616. Quite a change from a simple five- to seven-year experiment with "about 200 dogs" to study the plutonium/radium toxicity ratio!

Since the original purpose of the Utah Project was determination of the empirical ratios of toxicity of these several elements as compared to ^{226}Ra , let us look immediately at how it came out. Remember that it takes many years to accumulate reliable long-term toxicity information in an animal with a normal life span of fifteen years or more.

At the 1967 symposium at Sun Valley, Idaho, Mays et al. (1969) presented a fairly complete résumé of the findings to date. The survival times versus dose were presented graphically, and the RBE(a) relative to ^{226}Ra was given in much the same way as the data for rodents presented earlier in this chapter. They are reproduced here as figure 8.8A and B.

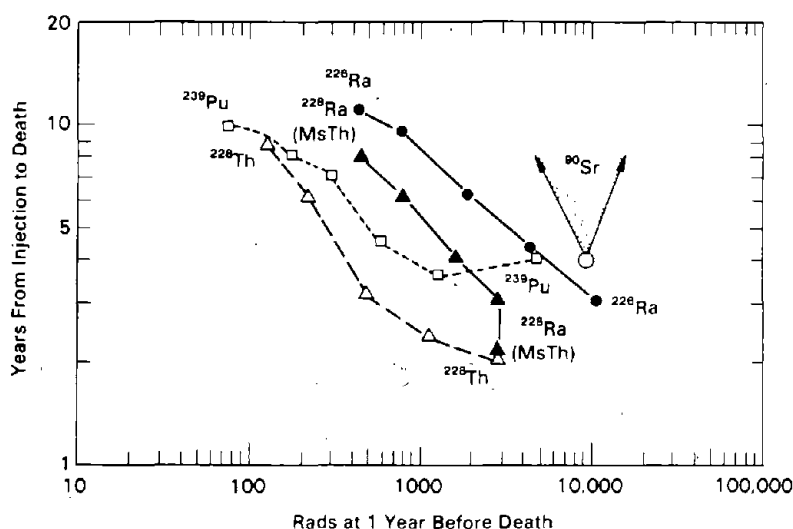


FIGURE 8.8A. Survival time versus dose for osteosarcoma beagles (March 1967). Each point is the average for the osteosarcoma dogs in an injection level. Connecting these points forms dose-survival curves for all nuclides except ^{90}Sr , for which the dose-survival curve lies between the limits shown by arrows. (Redrawn from Mays et al. 1969. Reprinted with permission of University of Utah Press, Salt Lake City, Utah, copyright 1967.)

The radiation dose was calculated as that to one year before death on the assumption that the tumor had been initiated a year before it killed the animal. The survival figures refer only to animals dying with osteogenic sarcoma, the principal cause of death.

A complete roster of the animals is given in a table in the cited publication along with a set of RBE values based on three criteria: rad at one year, at one year before death, and at death, for each element. These values are a function of the dosage level, much as we saw for the mouse earlier in this chapter. The data for strontium are quite tentative since that element was added to the experiment relatively late, and data were far from complete.

(a) See discussion of this terminology on page 387, footnote b.

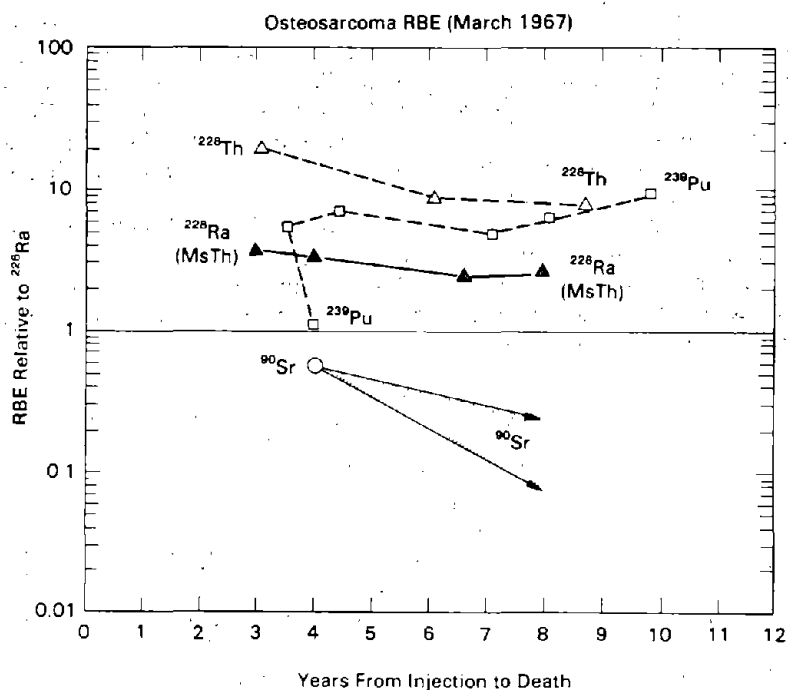


FIGURE 8.8B. RBE for death with osteosarcomas in beagles (March 1967) showing the effectiveness of ^{239}Pu , ^{228}Th , and ^{228}Ra relative to ^{226}Ra . That of ^{90}Sr is less and decreases further at long survival times. (Redrawn from Mays et al. 1969. Reprinted with permission of University of Utah Press, Salt Lake City, Utah, copyright 1967.)

For illustration, let us take the RBE values (i.e., toxicity or equal effectiveness ratios) for death with osteosarcoma eight years after injection using neither the highest nor the lowest dosage level. As calculated by Mays et al., these values are $^{226}\text{Ra} = 1$, $^{239}\text{Pu} = 6$, $^{228}\text{Th} = 8$, $^{228}\text{Ra} = 2.5$, and $^{90}\text{Sr} = 0.07$ to 0.24 . Comparing these to the ANL data on the mouse and the MED work on mouse, rat, and dog indicates a rather surprising agreement. Interestingly, ^{228}Th is the most effective in producing bone tumors at all but its lowest level, where it is comparable to ^{239}Pu . (See discussion of thorium in chapter 4.)

Ranges for the equal effectiveness ratio relative to ^{226}Ra over all three criteria and all five dose levels are: $^{239}\text{Pu} = 1.0$ at level 5 and dose to death; to 15 at level 1 and dose at 1 yr; $^{228}\text{Th} = 4.8$ at level 1 and dose to 1 yr, to 21 at level 2 and dose to death; $^{228}\text{Ra} = 2.4$ at level 2 and dose to death, to 6.5 at level 3 and dose to 1 yr; $^{90}\text{Sr} = 0.57$ at level 5 and dose to death, to >0.06 at level 5 and dose to 1 yr.

Of particular interest is the fact that the highest RBE for ^{239}Pu is at level 1, in the area of greatest interest for radiation protection purposes; and the surprisingly high effectiveness of ^{228}Th . The range of ratios is not large considering the many variables involved; and it is close enough to the earlier data to greatly strengthen any decisions regarding allowable exposures based upon the earlier work; yes, even the Tri-Partite Conference!

The prime cause of death with all of these elements was osteogenic sarcoma. Plutonium-239 seemed to retain its place as the most effective of all at low doses (i.e., long survival times), and the bone-surface seekers were, as a group, more effective than the volume seekers, just as in the mouse and rat.

The doses and dose rates in the beagle skeleton calculated to twenty years are shown in figure 8.9A and B for level 1 using the data accumulated through 1967.

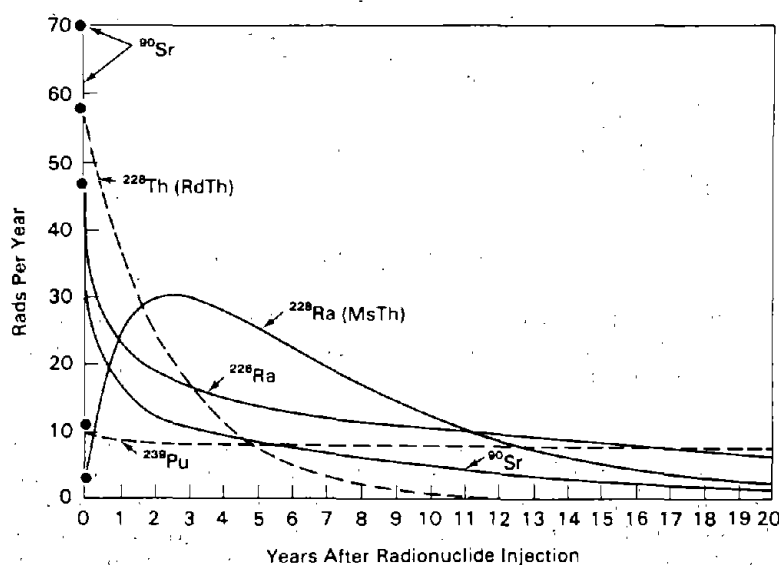


FIGURE 8.9A. Dose-rates in 1-level beagle skeletons. The 1-level injections were $0.0157 \mu\text{Ci } ^{239}\text{Pu/kg}$; $0.0152 \mu\text{Ci } ^{228}\text{Th/kg}$; $0.0505 \mu\text{Ci } ^{228}\text{Ra (MsTh)/kg}$; $0.0621 \mu\text{Ci } ^{228}\text{Ra/kg}$; or $0.571 \mu\text{Ci } ^{90}\text{Sr/kg}$. The dose-rate for ^{239}Pu remains fairly constant; that for ^{228}Th decreases primarily because of radioactive decay; that for $^{228}\text{Ra (MsTh)}$ increases initially due to the build-up of its alpha-emitting daughters—but it subsequently decreases because of radioactive decay and biological excretion; that for ^{228}Ra decreases because of biological excretion, while that for ^{90}Sr decreases because of both biological excretion and radioactive decay. (Redrawn from Mays et al. 1969. Reprinted with permission of University of Utah Press, Salt Lake City, Utah, copyright 1969.)

As time passed, attention was directed more toward understanding of mechanisms and expressing toxicity as a risk. Indeed, the quoted 1969 paper seems to be the last from Utah in which the ratio of toxicities is presented in the original form. (It was quoted by others long afterwards.) As a gauge of how the continuation of the experiment over additional years might influence the results, let us look at a report from 1979 (Mays et al. 1979). Using the points in the low-dose realm, the risk of osteosarcoma from ^{239}Pu was 5,200 bone sarcomas per 10^6 beagle-rad. The figure for ^{226}Ra was 320 bone sarcomas per 10^6 beagle-rad. The ratio is 16.25, assuming linearity of incidence to dose.

For the 1980 meeting of the International Radiation Protection Association, Mays and M. P. Finkel prepared a paper comparing alpha particles and beta

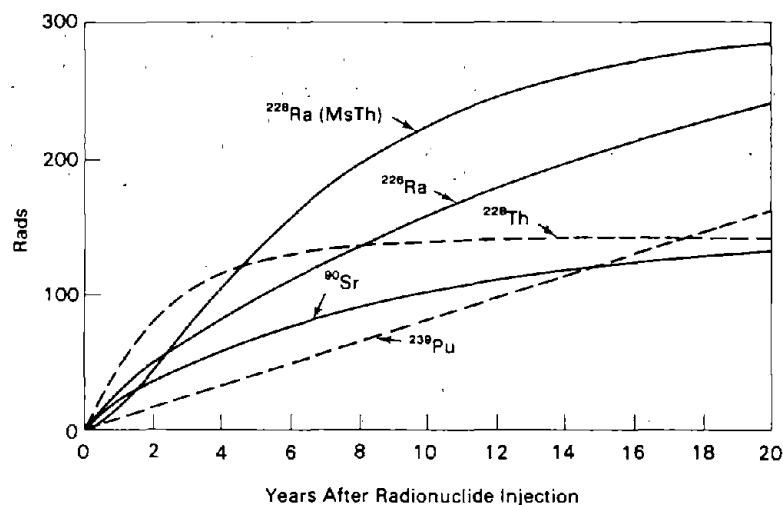


FIGURE 8.9B. Cumulative doses in 1-level beagle skeletons. (Redrawn from Mays et al. 1969. Reprinted with permission of University of Utah Press, Salt Lake City, Utah, copyright 1969.)

particles, with special emphasis on low doses and low risks. This bore especially on ideas gradually developing that the RBE rises with decreasing dose. When the results for ^{226}Ra and ^{90}Sr in Miriam Finkel's CF1 mice were compared with the accumulated data for the same elements in the beagles, the RBE clearly did rise as dose decreased. The relationships are shown in table 8.6 and figure 8.10.

TABLE 8.6. Bone Sarcoma RBE of ^{226}Ra Versus ^{90}Sr

Species	Incidence (%)	^{90}Sr β -particles (rads)	^{226}Ra α -particles (rads)	RBE (α versus β)
Beagles	66.7	9360	1900*	5
	38.5	8600*	1100	8
	16.7	7940	480*	17
	8.7	5500*	210	26
Mice	86.4	6500*	6420	1
	81.0	6300	4400*	1.4
	79.1	6200*	3640	2
	62.2	5500*	2040	3
	43.3	4600*	1190	4
	21.2	3700*	614	6
	23.4	3800*	480	8
	18.7	3500*	383	9
	13.6	3310	280*	12
	11.7	3100*	244	13
	7.7	2700*	109	25

*Interpolated from curves in text of paper.

Source: Reset from Mays and M. P. Finkel 1980.

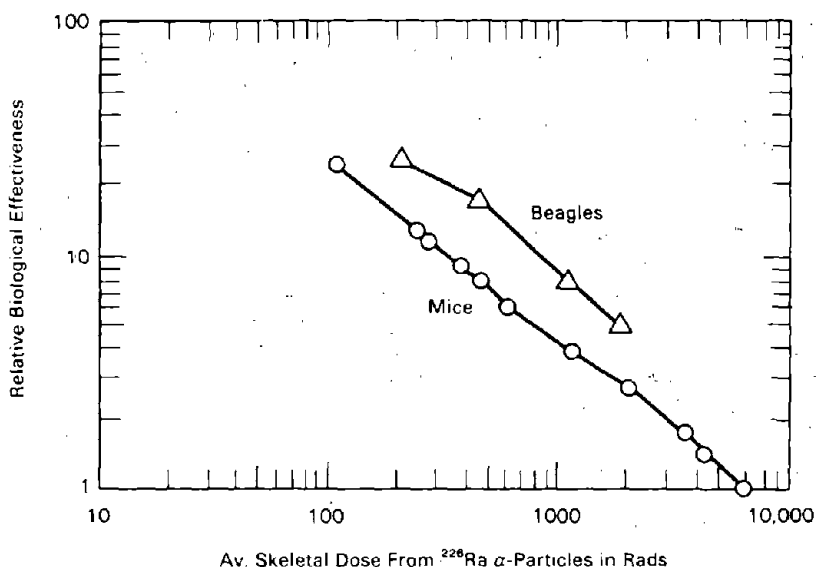


FIGURE 8.10. Relative biological effectiveness of alpha-particles from ^{226}Ra and retained daughters, relative to beta-particles from ^{90}Sr and its daughter, ^{90}Y . The RBE increases as dose decreases, both in beagles and in mice. The effect is mainly due to decreased effectiveness per rad in bone-sarcoma induction by beta-particles at low doses and low dose-rates. (Redrawn from Mays and M. P. Finkel 1980.)

The change in RBE is largely related to the change in effectiveness of the ^{90}Sr from lower to higher doses. In fact, the situation is much like the classic picture of low- versus high-LET external radiation sources.

The dental health of the beagles was followed assiduously and maintained well. Specific effects, beyond those connected with general oral health, which was not the best in this colony, appeared with ^{226}Ra , ^{228}Ra , and ^{228}Th . Excessive tooth loss was noted early (Taylor et al. 1961). Altered tooth and jaw structure appeared quite early too, followed by bone tumors (Dougherty et al. 1962b). These changes were comparable qualitatively to those seen in the radium dial painters and called "radium jaw" (chapter 1). See also Jee and Arnold (1960).

Marked gingival changes occurred also (Taylor et al. 1962). These included ulceration, infection, and other changes, again similar to those seen in the dial painters. These results are of special interest since rodents did not, in general, exhibit such marked deterioration of oral structures.

b. Effects in Soft Tissue

The deposition of plutonium and thorium in rodent liver has already been discussed. It was confirmed in the dog.

At the 1967 symposium, Taylor et al. (1969a) summarized soft tissue tumors in the population. Bile duct tumors, but no frank liver tumors, occurred in eight of

the animals receiving ^{239}Pu ; despite localization of the plutonium in other parts of the liver. Necrosis in liver was marked throughout the experiment.^(a)

Intraocular melanomas appeared in seven of the animals receiving ^{226}Ra or ^{228}Ra . (Remember the peculiar ocular changes reported in animals receiving radium, even in the MED days.)^(b) There was a sinus carcinoma in one dog receiving plutonium, one receiving ^{226}Ra , and one receiving ^{90}Sr . If a real finding, this casts doubt on radon as the prime causative agent for the sinus tumors in the dial painters. There were cancerous disturbances in the hematopoietic tissues as expected. But surprisingly these did not seem to be radiation-induced. The incidence of hemic and lymphoid tumors was significantly higher in the controls than in the irradiated groups. (This is not true in beagles receiving ^{90}Sr by feeding, as we shall see in a later section.)

At about the same time, kidney damage termed "radiation nephritis" appeared in the high-level ^{228}Th dogs.

Taylor et al. mentioned the occurrence of a "wide range of benign and malignant growths" in soft tissue, which were "clearly" a normal phenomenon and not caused by the deposited isotopes. The Utah workers were in fact so sure that these changes were not related to the deposited radioisotopes that they excised many such growths "before they could become serious clinical problems." In this respect, the dog work differs from the rodent work, in which treatment of any kind was characteristically withheld. Only in a population whose normal aging and disease behavior is very well known can the experimenter have the courage to intercede with treatment—another tribute to the planning of an ample control population and the presence of hundreds of similar dogs in other colonies about the country.^(c)

c. Hematology Findings

In the ten-year report (Dougherty et al. 1962b), early depression of white cell counts was general at all levels. At the lower doses, return to normal occurred to a greater or lesser degree. Thorium-228 caused more profound and more sustained depression of blood-cell formation at higher dose levels than did any of the other elements. The platelets followed the lymphocyte pattern in general, while the effect on red cells varied more among the radionuclides. In general, there was an early transient anemia, but only at later times was there progressive and serious anemia, and this only in the high-level dogs. Thus, reduction of circulating blood cells and damage to the blood-forming system do not seem to be sufficient in themselves to cause death at the levels of interest to this work.

- (a) Recently, the incidence of liver tumors in other experiments has led some investigators to speculate that liver changes may play a more central role in the toxicity of these elements than the original Utah dog experiments indicated. This requires more information since many of the effects are from Thorotrast, which may involve a factor of chemical toxicity. (See chapter 4 for further discussion and an update.)
- (b) Mays et al. showed that radium isotopes concentrate in the melanocytes of the eye. Later it became clear that these ocular lesions appeared at lower doses of ^{226}Ra than were needed to include bone sarcoma. No such lesion has been seen in the eye of man or primates.
- (c) The nuances of this procedure are taken up in some detail in one of the quarterly reports (Taylor 1965). The general health of the colony and prolongation of life span to allow expression of the really long-term effects were paramount. Only bone changes, signs of osteogenic sarcoma, or other entities clearly associated in the past with ionizing radiation effects, were left without the best of therapy, and no animal was allowed to suffer unduly.

Dougherty and Rosenblatt summarized the long-term hematological changes for the five key elements in 1971. There was great similarity of effects among the nuclides, but some quantitative differences. They give "median hematological RBE's"^(a) for the first year postinjection using $^{226}\text{Ra} = 1$ as: $^{228}\text{Th} \approx 4$; $^{239}\text{Pu} \approx 4$; $^{228}\text{Ra} \approx 2$; and $^{90}\text{Sr} \approx 0.5$. While in the same direction as their relative effectiveness in bone, the differences are in general smaller. The extra effectiveness of plutonium and thorium is attributed to their ability to irradiate bone marrow from their deposition sites on bone surface.

Blood chemistry findings, while showing many changes, were not interpretable as more than reflecting the changing clinical status of the animals.

d. Retention and Dosimetry

The reader will note that the doses in figures 8.8.A and 8.9A,B are given in rad. This contrasts to the practice in ANL work where the dose is characteristically given as administered dose in $\mu\text{Ci/kg}$. The reason for this is partly that the Utah group was strongly influenced by the physicists and chemists in their midst who wanted to get down to physical quantities. But it is also partly due to the great care taken in measuring retention and distribution. Remember *three* measures were used.

Equations for retention and excretion began to appear with the earliest moderately complete results. Each additional group of animals and passage of time allowed elaboration and improvement of the functions. These are updated in each semiannual and annual report.

In the 1961 symposium volume, Stover, Atherton, and Mays (1962) present data for the first thousand days for ^{226}Ra , ^{228}Ra , ^{239}Pu , ^{228}Th , and ^{90}Sr showing total retention, plasma concentration as a function of time, and, of course, skeletal retention. Some of these are outlined below.

Parent Nuclide	Decay Products	Total Retention(a)	Skeletal Retention(b)
Ra^{226}		$R = 0.79t^{-0.20}$	$B \approx R$
	Rn^{222}	$R = 0.045$	$B \approx R$
Pu^{239}		$R = 0.90 - 0.0043t^{0.52}$	$B = 0.72t^{-0.04}$
Ra^{228}		$R' = 0.79t^{-0.20} e^{-\lambda t}$	$B' \approx R'$
Th^{228}		$R' = (0.19e^{-0.0011t} + 0.69)e^{-\lambda t}$	$B' \approx 0.65e^{-\lambda t}$
	Ra^{224}		$B' = 0.53e^{-\lambda t}$
	Tn^{220} and its decay products		$B' \approx 0.45e^{-\lambda t}$
Sr^{90}		$R' = 0.68t^{-0.21} e^{-\lambda t}$	$B' \approx R'$
	Y^{90}	$R' \approx 0.68t^{-0.21} e^{-\lambda t}$	$B' \approx R'$

(a) Fractional Retention ($R' = R e^{-\lambda t}$).

(b) Biological Fractional Skeletal Retention (B).

Fractional Skeletal Retention ($B' = B e^{-\lambda t}$). (b)

Biological Fractional Retention (R)

(a) The ratio of dose rates from a radionuclide that produces a 50% depression in blood cells using the dose rate from ^{226}Ra required to produce the same effect as unity.

(b) This is reproduced as in the original. It should probably be $B' = B e^{-\lambda t}$.

Thus, we see something of a mixture of the power function seen in the ANL and some other studies, including data for man with ^{226}Ra and a modified exponential. The most complex function is for the most complex element, ^{228}Th . Each of these was determined by empirical fits to the data and represents a generalization. These are translated to doses to the skeleton in the ten-year summary paper by Dougherty et al. (1962a,b).

A review of the equations and procedures was produced as a separate Utah Project report (Lloyd 1970) and in annual reports for 1977 (COO-119-252), 1978 (COO-119-253), and 1979 (COO-119-254). It is of interest to note that there was considerable variation in retention and that the dose had to be calculated for each individual dog for ^{226}Ra , ^{228}Ra , and ^{90}Sr (and in the later work also for ^{241}Am , ^{247}Cf , and ^{252}Cf). But for ^{239}Pu , ^{228}Th , and ^{224}Ra , a single composite function could be applied based on average skeletal retention equations. Much of the same material was presented in the open literature by Lloyd et al. (1976). As the total time approached fifteen years or more, the preferred representation became a series of exponentials with no power function component. This is not surprising, for as more and more points were gathered, the true nature of the relationship could be set out for functions which with fewer points looked like a power function.

Some typical retention curves with both average and individual curves can be viewed in the 1970 report and 1976 publication. The actual equations taken from the 1979 annual report are shown in table 8.7.

These equations are for either an average animal or an individual and were utilized for most of the dose calculations. Obviously they give average dose. Much work was done in the Utah group, as elsewhere, to determine the target cells (e.g., endosteal cells for bone cancer) and the probable dose to them. These efforts included quantitative autoradiography, some using alpha track counting methods (Sears, Jee, and Mays 1962; Jee et al. 1969; Taylor et al. 1969b; Jee, Dell, and Davis 1971; Smith et al. 1977); electron microscopy of the effects (Whitson and Jee 1971); careful calculation for the ranges of alpha particles and microscopically determined sites of localization (Mays 1958 and 1960; Mays and Sears 1962; Mays and Tueller 1964); and the usual analysis of macrodistributions among bones and major subdivisions of other organs.

Each of these papers, or the ideas pertinent thereto, has been presented also in the open literature, sometimes in less detail than in these project reports. They are too numerous and extensive to cite here. The anniversary volumes are listed at the end of this section. A harbinger of the depth and quality of publications to come can be seen in the paper by Jee et al. in the tenth anniversary symposium in 1961 (Jee et al. 1962). They were still at it for the twenty-fifth anniversary volume (cf, e.g., Stover 1976) and in the 1969 and 1975 IAEA symposia.

These studies and derivations are still undergoing refinement for such factors as dose rate, age effects, species differences, even strain differences. In the following section, we will review some of these and other ramifications of the Utah Project that have carried it considerably beyond the initial concept.

8. Extensions of the Utah Project

It is almost inevitable that a project as large and complex as the Utah undertaking would generate the need for more work to follow through on ideas generated en route. We can take space to review these only by a somewhat cursory listing.

TABLE 8.7. Retention Equations^(a) for Nine Elements in the Beagle as of 1979

$^{226}\text{Ra} = 0.412e^{-0.558t} + 0.105e^{-0.0730t} + 0.196e^{-0.00488t} + 0.287e^{-0.000299t}$ (5-level only)
$^{226}\text{Ra} = 0.251e^{-0.982t} + 0.211e^{-0.269t} + 0.210e^{-0.0155t} + 0.177e^{-0.00204t} + 0.151e^{-0.000150t}$ (lower levels)
$^{222}\text{Rn}/^{226}\text{Ra} = 0.075 (1 - e^{-0.181t}) t^{0.158}$ (all levels)
^{239}Pu (dose level 5) = $0.07e^{-0.0011t} + 0.43$
^{239}Pu (dose level 4) = $0.11e^{-0.0011t} + 0.39$
^{239}Pu (dose level 3) = $0.15e^{-0.0011t} + 0.34$
^{239}Pu (lower levels) = $0.29e^{-0.0011t} + 0.21$
$^{228}\text{Ra} = 0.251e^{-0.982t} + 0.211e^{-0.269t} + 0.21e^{-0.0158t} + 0.177e^{-0.00237t} + 0.151e^{-0.000479t}$ (pure at $t = 0$)
84% retention of <i>in vivo</i> produced ^{228}Th and daughters. ^(b)
$^{228}\text{Th} = 0.69e^{-0.00113t}$
$^{224}\text{Ra}/^{228}\text{Th} = 0.895$
$^{212}\text{Pb}/^{228}\text{Th} = 0.866$
$^{90}\text{Sr} = 0.36e^{-0.95t} + 0.29e^{-0.12t} + 0.10e^{-0.0092t} + 0.12e^{-0.0020t} + 0.13e^{-0.00022t}$
^{241}Am (dose level 5) = $0.359 + 0.157 (1 - e^{-0.0065t})$
^{241}Am (dose level 4) = $0.359 + 0.141 (1 - e^{-0.0029t})$
^{241}Am (dose level 3) = $0.359 + 0.076 (1 - e^{-0.0021t})$
^{241}Am (lower levels) = $0.359 + 0.015 (1 - e^{-0.0014t})$
$^{249}\text{Cf} = 0.498e^{-0.0000794t}$
$^{252}\text{Cf} = 0.498e^{-0.000791t}$
$^{224}\text{Ra} = 0.528e^{-0.214t} - 0.228e^{-9.01t}$ with the effective retention of ^{224}Ra daughters of: ^{220}Rn and $^{216}\text{Po} = 0.486e^{-0.214t} - 0.276e^{-4.65t}$ $^{212}\text{Pb} = 0.447e^{-0.214t} - 0.336e^{-2.40t}$ $^{212}\text{Bi} = ^{212}\text{Po} + ^{208}\text{Tl} = 0.391e^{-0.214t} - 0.350e^{-2.38t}$

(a) These include both radioactive decay and biological elimination. Thus, times calculated therefrom are *effective retention times*.

(b) The ^{228}Ra figures include contribution from ^{228}Th contamination in the injection solutions and are based on the newly determined half-life for ^{228}Ra of 5.77 ± 0.02 years.

Source: Reset from Utah Report COO-119-254, *Research in Radiobiology*, Annual Report, 31 March 1979, Appendix p. A-4, A-5.

- a. The need to add new dosage levels and what they were has already been described.
- b. Americium-241 was added for the reasons described in section VII. Curium-244 and -243 were added at about the same time with studies in mice reported much later (1976).
- c. Californium-249 and -252 were added considerably later for comparison with plutonium and radium. Californium-252 decays by spontaneous fission in a few percent of its disintegrations and thus has been proposed for possible neutron sources of very small size. Production in considerable quantities is anticipated (Seaborg 1973). The isotope ^{249}Cf is an alpha emitter and should have metabolic properties identical to ^{252}Cf . Thus, a direct comparison of an alpha emitter and a fission fragment was possible. Also, the discrete gamma rays of ^{249}Cf (333 and 388 keV) allowed for easy tracing of its movements in contrast to the more or less continuous gamma spectrum of ^{252}Cf . Early results were presented in a series of articles in the annual report for 1971 (Lloyd et al. 1971; Dougherty 1971; Taylor et al. 1971; Stevens and Bruenger 1971a,b; etc.). Berkelium-249 was used briefly for a soft tissue localization experiment. Discussion of results of these and many other experiments with transplutonic elements is reserved for a special section.
- d. Radium-224 was entered quite early for comparison of a short-lived radium isotope that would deliver most of its energy at the point of initial deposit, bone surface, with the much longer-lived ^{226}Ra , which soon gets buried by bone growth and turnover. This was well before discovery of the German patients and the findings reported in chapter 1. Because of the studies of German patients, a new and larger experiment with ^{224}Ra in the beagles was added. The results followed the pattern already described in chapter 1.
- e. To get a better grasp of age effects, especially with plutonium, groups of animals were added with injection occurring at three months or at five years of age in contrast to the standard seventeen-month-old animal. Results of these ramifications are still quite incomplete. Some early indications are given by Jee et al. (1975).
- f. Polymeric plutonium was substituted for the monomeric plutonium citrate to check on the role of mobilized deposits from the liver in increasing the initially very low bone deposition and on bone as compared to liver pathology.
- g. Plutonium-238 was studied for intraorgan distribution in the cynomolgus monkey (reported in 1977).
- h. The skeletal toxicity of plutonium in a group of St. Bernard dogs was tested for comparison with the beagle. The St. Bernard has a high natural incidence of bone tumors compared to the almost zero natural incidence in the beagle. There appeared to be a direct relationship between spontaneous and radiation-induced sensitivity. The latent period for tumor induction in the St. Bernard has been less than one-half that in the beagles in the results so far. Fortunately, this did not seem to foster a compulsion to make the St. Bernard the animal of choice for further work!
- i. The deer mouse and the grasshopper mouse were introduced for pilot studies as rodents that might be more suitable for long-term work than the usual laboratory strains.
- j. Because of accusations that possible genetic changes were not being properly evaluated in this huge enterprise, a special effort was made to determine again, and more precisely, the concentrations of transuranium elements in gonadal tissue (Mays, Lloyd, and Atherton 1974). There will be more

discussion of this in later chapters, even though the concentration in gonads was vanishingly small in the case of the actinides.

9. Concluding Comments—Anniversary Volumes

The Utah Project has gone far beyond its original concept and has provided toxicity information to meet all of the empirical needs. It must be remembered, however, that most of the work represents the results of a single intravenous injection. Other projects have attacked the ingestion and inhalation routes. But all have met around the insights provided into the mechanisms of handling bone-seeking radionuclides in living organisms, tissues, and cells, and a few revelations regarding some of nature's most closely guarded secrets—the mechanisms of carcinogenesis. In chapter 21 we will review a few of these.

The symposia and special publications that occurred on or around significant anniversaries in the life of the Utah Project are listed below with their published volumes. The times are approximate and have some slippage according to when one chooses to consider that the project started and when they managed to get an international group together.

Symposium	Publication
1. Second Annual Conference at University of Utah, 1954	<i>Second Annual Conference on Plutonium, Radium and Mesothorium.</i> C. N. Stover, Jr., ed. AEC Report, TID-7639.
2. Ten Years Heber, Utah, May 8-11, 1961	<i>Some Aspects of Internal Irradiation.</i> J. H. Dougherty, W. S. S. Jee, C. W. Mays, B. J. Stover, eds. Pergamon Press, New York-Oxford 1962
3. Fifteen Years Sun Valley, Idaho, September 12-14, 1967	<i>Delayed Effects of Bone-Seeking Radionuclides.</i> C. W. Mays, W. S. S. Jee, R. D. Lloyd, B. J. Stover, J. H. Dougherty, G. N. Taylor, eds. University of Utah Press, Salt Lake City, 1969
4. Twenty Years University of Utah, October 1970, Honorary Degree Ceremony for Glenn Seaborg	<i>Radiobiology of Plutonium.</i> B. J. Stover, W. S. S. Jee, eds. J. W. Press, Salt Lake City, 1972
5. Twenty-Five Years Sun Valley, Idaho, October 6-9, 1975	<i>Health Effects of Plutonium and Radium.</i> W. S. S. Jee, ed. J. W. Press, Salt Lake City, 1976.

To determine the Utah contributions, it is suggested that the names attached to the references for this section of this chapter be searched out. Remember that many of the Utah symposia, particularly in later years, embraced much more than Utah results. Indeed, as the Project matured, these meetings became prominent among the correlators, as well as the data contributors.

The "Founding Fathers," all but one (Langham), remained actively concerned with the project, and met in advisory capacities for several years. But it is clear that the undertaking conceived thirty years ago is fully mature and now with a new Director, Dr. McDonald E. Wrenn, recently of New York University, is ready to carry its ideas into still other fertile fields, provided funding continues.

C. The Davis Beagle Project

At almost the same time as the Utah Project was being organized, the School of Veterinary Medicine at what is now the University of California at Davis undertook a study of the consequences of graded and fractionated exposures to x-irradiation in the beagle. The chief objective was the study of reproductive performance. But many other measures were added.

At this time (early 1950s), Davis was the Agricultural Experiment Station or University Farm in the California system^(a) and a good site for a beagle colony. In fact, it may well be that the first proposals anywhere for use of the beagle dog in long-term king-sized experiments came from George Hart, then Dean of the Veterinary School at Davis. The origin of the idea for this project is not as clearly documented as for the Utah Project. A contract was let in January 1951 for the external radiation work. This was placed in the hands of a young veterinary protégé of Dean Hart, A. C. ("Bud") Anderson, with help from some other veterinarians (Hal Parker, John Luick) and some biometricians (L. Rosenblatt, Fred Schultz). The first step was development of a breeding colony followed by many years of operation as AEC "Project Four" for the external radiation work.

The proliferation of problems from the fallout attendant upon nuclear weapons testing made urgent the gathering of knowledge on the metabolism and effects of radionuclides after *ingestion* for long periods, i.e., an experiment more imitative of actual exposure conditions than the Utah Project. Utilizing the presence of the large and growing beagle colony at Davis seemed appropriate for an ingestion study to parallel the intravenous work at Utah.

In 1956, the AEC negotiated a contract with the school for "Project Six" in which suitable numbers of beagles were to receive ⁹⁰Sr in their daily food. The work began initially under A. C. Anderson, but later a radioisotope man, Leo Bustad from Hanford, and some other staff with background in internal emitter research, were brought in (see Appendix B).

Although we hear much less about it, there seem to have been some "Founding Fathers" for the Davis Project as there were for Utah. Indeed, some of the same people appear: Austin Brues and Wright Langham initially, followed very soon by Robley Evans and Harry Blair. H. D. Bruner of AEC Washington carried much of the organizing and planning burdens. It is reported that the early meetings of this group even utilized a court stenographer with the usual reams of unmanageable notes resulting (Goldman 1980).

The unit level (i.e., No. 1 level) of the Davis experiment was planned to be identical dosimetrically to the 1 level in the Utah Project. Work was started in a borrowed U.S. Air Force trailer. The exposures began essentially at conception and continued until the animals were 540 days of age. Thus, this experiment differed from the one at Utah, not only in utilizing the ingestion route, but in having essentially continuous intake for an appreciable period.

To tie further to the Utah project, and to the experiences in humans, a series of animals were given ²²⁶Ra. But these were given not orally or as a single injection, but in a series of eight semimonthly intravenous injections starting at 435 days of age, comparable to the time the Utah dogs (first phase) received their single injection. For further cross-referencing purposes, a smaller series of dogs received ⁹⁰Sr in a single intravenous injection at 540 days of age.

(a) It did not become an official campus of the university system until 1959.

There were morphologic studies of bone utilizing a variety of techniques: microdosimetry, cytogenetics, and forays into bone marrow culture and immunologic research. All of these were in addition to the conventional life-span, tumor-incidence, and clinical studies.

In 1973, Dr. Bustad left Davis to become Dean of the Veterinary School at Washington State University, his alma mater. Dr. Marvin Goldman, who had had in-depth experience with strontium research from the days of his doctoral thesis and other research at Rochester, took over.

Table 8.8 shows the dosage levels and general protocol of the experiment as of 1973. It did not change much thereafter. Note that the factors between the doses are comparable to those in the Utah Project.

TABLE 8.8. Davis Beagle Project: Experimental Design of Radionuclide Toxicity Studies

²²⁶ Ra Injection Series (Eight Semimonthly IV Injections Starting at 435 Days of Age)				
Treatment Code	Multiple of 1 level	Avg/Injection (μ g)	²²⁶ Ra (μ g/kg)	Number of Dogs
R00	0	0.00	0.000	81
R05	0.3	0.03	0.003	46
R10	1.0*	0.08	0.008	38
R20	6	0.05	0.047	41
R30	18	1.4	0.14	39
R40	54	4	0.42	41
R50	162	12	1.25	38
				324
⁹⁰ Sr Ingestion Series (in utero to 540 Days of Age)				
Treatment Code	Multiple of 1 level	Avg Ingested/day (μ Ci)	⁹⁰ Sr (μ Ci/g dietary Ca)	Number of Dogs
D00	0	0.00	0.000	79
D05	0.3	0.03	0.007	75
D10	1	0.08	0.021	42
D20	6	0.5	0.123	64
D30	18	1.5	0.37	70
D40	54	4	1.11	56
D50	162	12	3.33	47
D60	486	36	10.00	19
				452
⁹⁰ Sr Injection Series (Single IV Injection at 540 Days of Age)				
Treatment Code	Multiple of 1 level	⁹⁰ Sr (μ Ci/kg)	Number of Dogs	
S20	6	3.7	19	
S40	54	33	25	
			44	

* This level was computed to represent the canine equivalent of ten times the Radiation Protection Guide value for man (0.1μ g ²²⁶Ra).

Source: Reset from 1973 Annual Report, Radiobiology Laboratory, UCD 472-120.

Since the Davis work on radioisotopes was developed entirely as a result of the problems of fallout from nuclear weapons testing, details of the results belong properly in chapter 13 and will be reserved for that discussion. Our interest here is the general design of the project for comparison with the other large beagle experiments. It is interesting to note that ^{226}Ra was again the benchmark, but after multiple rather than single injections, while there was a single-injection strontium group for direct comparison with Utah. But the main thrust was ingestion over a long period, which included gestation and infancy. Thus, several new variables were added, but the "Founding Fathers" and the local staff felt they had sufficient ties into other experiments to minimize any possible variations due to strain of animal, experimental conditions, etc.

The Davis Project did not formalize its anniversaries to the same degree as the Utah group. Their contributions will be obvious in chapter 13. But they did sponsor one major symposium, which came out as a separate publication, *Biomedical Implications of Radiostrontium Exposure*, edited by Marvin Goldman and Leo Bustad and issued as one of the AEC symposium series books (Goldman and Bustad 1972).

The Davis Project has now become an integral part of the University of California, Davis, School of Veterinary Medicine, has contributed considerably to knowledge of fundamental mechanisms, as well as the initial programmatic goal, and is now undertaking work related to a variety of nonnuclear energy sources. Its staff and students are also an integral part of the teaching program of the school.

Perhaps because of the initial orientation of the campus and its strong ties to the veterinary school, the work at Davis has produced a number of important papers on general aspects of the development of large animal colonies for research and that often neglected, but vitally important topic, the role of the animal caretaker in the success of such undertakings. Beside the truism "Blessed is the researcher or administrator who has a fine secretary" should go, for those involved in any long-term animal study, "Blessed is he (or she) who has an intelligent and dedicated animal care establishment." Agricultural communities are more likely to be so blessed.

D. The Lovelace Project

The last of the de novo king-sized experimental installations for internal emitter toxicology was developed at what was then known as the Lovelace Foundation for Medical Education and Research in Albuquerque, New Mexico. Work on the inhalation of elements that emit alpha particles, such as plutonium, polonium, uranium, and radon and its decay products, was under way at Hanford and Rochester as we will review in the chapter on inhalation toxicology. But despite the importance of the inhalation route, relatively little work was being done on the long-term effects of inhaled fission products. This was not surprising, for very special facilities were required to handle aerosols of these beta- and beta-gamma-emitting elements.

Largely at the instigation of H. D. Bruner at AEC Headquarters, and with important assistance from Dr. C. W. Shilling, deputy director of the Division of Biology and Medicine, it was decided to develop yet another large project centering on beagles to get the much needed information on fission products. Because of possible radioactivity hazards, an isolated site was desirable. Hanford had the isolated sites, but was already working at capacity. Rochester was far

from isolated and not a good site for such a program. The Lovelace Foundation, itself located close to the edge of the desert in Albuquerque, had been conducting extensive work for the Air Force on blast biology and had use of an area of the Sandia Base a few miles from the clinic. The blast biology work was winding down, and W. Randolph Lovelace, Jr., son of the founder of the clinic, evinced interest in some new work. After the usual meetings and probings, a decision was made to build and staff a facility then called the "Fission Product Inhalation Studies" in the desert not far from the earlier facility. While the clinic staff was oriented primarily to clinical medicine, there was much talent available in the area for consultation and help in developing staff, since both the Kirtland and Sandia bases were closely associated with the weapons programs.

Lovelace (Randy) placed C. S. (Sam) White, who had headed the blast biology work, in charge of developing the facilities and gathering a staff. A purebred beagle colony was established in 1961 using dogs from some of the other large AEC projects and also commercial breeders. The details of development and the care and breeding of this colony have been given by Redman et al. (1970).

A unique facility was created, which, among other things, utilized the abundant evaporative potential of the desert climate to greatly reduce the volume of liquid waste requiring disposal by the use of open holding ponds. Good separation of "hot" and "cold" operations was facilitated by the abundance of land to spread out upon.

In due course, the staff was assembled, many of them trained at Rochester in aerosol physics and inhalation toxicology and pathology. There were no formal "Founding Fathers," but there was considerable exchange with other laboratories doing inhalation work, accomplished through the AEC Headquarters staff, particularly Dr. William Lotz who had assumed some of the administrative work for the internal emitter research with H. D. Bruner. A group called the "Inhalation Toxicology Working Group" met rather frequently at the cognizant laboratories. Some meetings of this group placed special emphasis on the plans for the Lovelace experiments.

With the death of Randy Lovelace, Sam White had to assume broader responsibilities, and a full-time director was needed for the inhalation program. Fortunately, Dr. Roger O. McClellan, a veterinarian who had had experience for many years at Hanford, and also a tour of duty at AEC Headquarters, was persuaded to go to Albuquerque in 1966, and the laboratory has grown, diversified, and prospered ever since.

In the early 1970s, the several parts of the Lovelace organization were consolidated as the "Lovelace Medical Foundation." The inhalation research became a subsidiary corporation of the Foundation, the Inhalation Toxicology Research Institute (ITRI), to recognize that its interests and work had gone into areas beyond the original fission product research. And finally, as the general program broadened still more to include environmental contamination problems with both radioactive and chemically toxic pollutants, the parent organization became The Lovelace Biomedical and Environmental Research Institute.

The work was not confined to the dog, especially for aerosol and short-term toxicity studies. We will review it in chapter 9.

The primary thrust of the results pertain, of course, to the inhalation route of exposure and its special problems. Thus, discussion of the findings and their relation to other inhalation toxicology programs will be reserved for chapter 9. Key personnel in the organization will be found in the publications listed in that chapter and also, briefly, in Appendix B.

IV. Almost New Projects: Hanford and Los Alamos

In chapter 7, we had only a glimpse of the wartime work at Hanford because it was largely monitoring plus a rather extensive environmental program, which we will review in chapter 11. We also looked very briefly at the immediate postwar aspects that were tied directly to the World-War-II operations. In essence, both of these activities were centered on personnel or environmental monitoring, except for the important bio-effects program at Hanford in aquatic biology.

Very soon after the organization of the AEC, i.e., in 1947, both Hanford and Los Alamos expanded greatly in the field of biomedical research, as contrasted to monitoring and worker protection. Since these expansions were built upon an existing core of personnel and ideas, they cannot be regarded as "new" projects in the sense that Utah, Davis, and Lovelace were established *de novo*. But they were different enough from the wartime effort to be regarded as "almost new." Both Hanford and Los Alamos have contributed enormously to fission product and actinide studies, as well as in other areas, throughout the 1950s, 1960s, and 1970s. We will review briefly their growth and contributions in turn in the next two sections of this chapter.

A. The Hanford Biology Operations^(a)

1. Immediate Postwar Developments

In the late 1940s, Herbert M. Parker, who headed the Health Instruments (HI) Division of the Hanford Works throughout the war years, initiated expansion into a practical program in radiobiology linked to the hazards to humans and the environment that had arisen in their work. Karl Herde and Dick Foster had been in the environmental work for many years, but as a division separate from HI. In fall 1946, these operations were consolidated as a biology section under the Radiological Sciences Division, which Parker headed. In 1947, Harry Kornberg came aboard to head a biochemistry section, and before long he became manager of the entire biology operation. P. L. Hackett, L. K. Bustad, R. F. Palmer, S. Marks and other names we associate with long tenure at Hanford appear in the first annual report covering the year 1951.

Facilities were made available rather quickly by renovation of a sizeable building near one of the production reactors. This was "onsite," which at Hanford meant about thirty miles from the town of Richland. There was ample space for construction of satellite facilities for holding and care of large animals. Its isolation made the possible contamination of inhabited spaces much less of a worry than had it been close to town or on a university campus. But it also meant an onerous trip for personnel needing to observe or care for animals at odd hours.

2. Iodine and Sheep

One of the first major experiments concerned ¹³¹I. During the war years, environmental surveys around the reactors had shown its presence, and monitored rabbit thyroid glands had confirmed significant, though not dangerous, concentrations therein. Iodine appeared to be more prevalent in the reactor off-gases

(a) Later Pacific Northwest Laboratory (PNL), operated by Battelle Memorial Institute.

than most of the other fission products. Leo Bustad, a competent veterinarian and researcher, spearheaded the iodine work. They chose sheep rather than dogs as the experimental subject, perhaps because the real problems at sites like Hanford, indeed most reactor sites as then known, could easily involve large herds of grazing animals. Also, the limiting hazard was deposition on vegetation and intake by grazing animals rather than direct inhalation.

The first Hanford annual report in biology (Report HW-25021, 1952) gives a general description of a low-level chronic-effects experiment, histopathology of the thyroid gland and the changes in blood constituents (i.e., clinical chemistry). Reports on this iodine experiment with sheep appear in every annual report up to 1961, and occasionally thereafter. The bulk of the work involved feeding the contaminant to the sheep to tie as closely as possible to problems in the field. The results are nicely summarized in a special paper published in *Radiation Research* (Bustad et al. 1957) and along with work from other laboratories in the Hanford biology symposium held in June, 1963, and published in *Health Physics* (Bustad 1963).

This project was not only the first long-term experiment with iodine in a large animal, but probably the first project to get under way involving multigeneration, chronic administration of a radioisotope to a large animal. It was started in April 1950 with ewes in an advanced stage of pregnancy. The iodine was added to the feed in the form of drilled pellets and administered daily. Selected offspring were placed after weaning on the same regimen, and most groups continued for at least three generations.

The levels administered in both the initial and subsequent phases are summarized in table 8.9. The lowest level (0.005 $\mu\text{Ci/day}$) was calculated to deliver a dose rate to the thyroid, after uptake of 0.3 rad/wk, equal to the maximum permissible exposure to whole-body penetrating radiation in humans. The other levels were chosen arbitrarily to cover a considerable range in order to establish the thyroid ablative dose.

TABLE 8.9. Experimental Design for Hanford ^{131}I Experiment with Sheep

	Level $\mu\text{Ci/day}$	Number of Sheep
Initial Experiment	1800	3
	240	12
	5	12
	0.15	24
	0.005	24
Project Controls		24
Offsite Controls		20
Additions	135	5
	45	5
	15	5

Source: Modified from Bustad et al. 1957. Reprinted with permission of Academic Press, Orlando, Florida, copyright 1957.

The 1,800- and 240- $\mu\text{Ci/day}$ levels were found to produce complete destruction of the gland and were discontinued after 420 and 450 days, respectively. The lowest level, 0.005 $\mu\text{Ci/day}$, was discontinued when it became clear that even the 0.15- $\mu\text{Ci/day}$ level was apparently without observable effect. Intermediate levels of 135, 45, and 15 $\mu\text{Ci/day}$ were inserted to get more information in the region between ablation and no effect.

A flowchart for the experiment is reproduced as figure 8.11 taken from Bustad et al. (1957). The results appeared not only in the special summaries already cited but also in the annual reports over a number of years. They were not conspicuous in the routine literature, being better suited to larger compendia. The results are described briefly below:

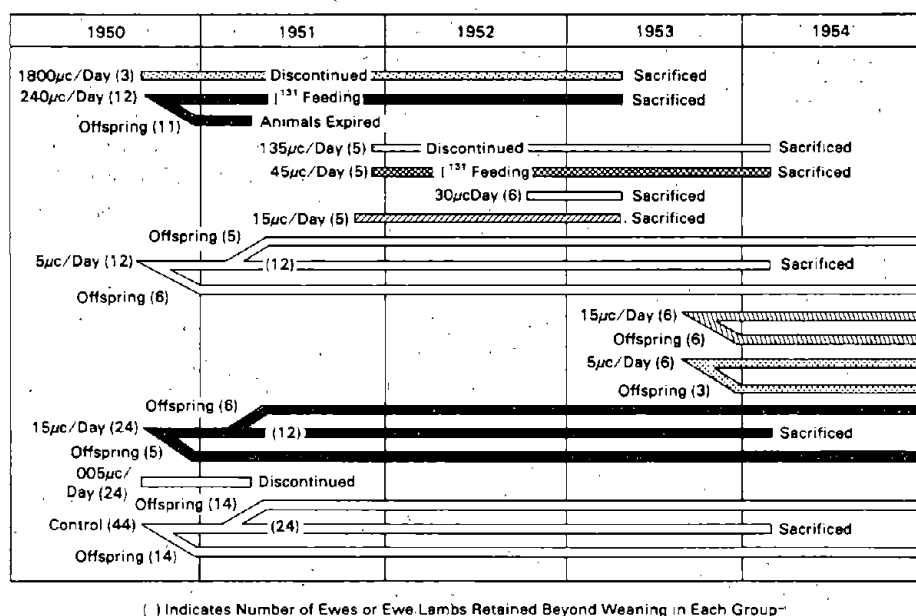


FIGURE 8.11. Experimental design for Hanford experiment with ¹³¹I in sheep. (Redrawn from Bustad et al. 1957. Reprinted with permission of Academic Press, Inc., Orlando, Florida, copyright 1957.)

1. Thyroid activity was diminished in all ewes fed 5 μ Ci, or more, per day. External monitoring showed this well ahead of the development of clinical symptoms.
2. Specific damage was caused by ¹³¹I in structures close to the thyroid, and there was ulceration of the mouth and lymphopenia. Otherwise the effects of ablative doses produced changes similar to surgical ablation of the thyroid.
3. Systemic clinical manifestations were, in general, those of thyroid deficiency.
4. Conception and breeding seemed normal in the first generation, but ewes in the second generation failed to produce live offspring at the two highest levels. Reproductive performance was surprisingly good at the lower levels, even in the presence of some thyroid damage.
5. Uptake of ¹³¹I by the thyroid was fairly avid in the low-dose groups because the basic diet was marginally goitrogenic (by design). It was highly variable in the treatment groups because of significant damage. Uptake of ¹³¹I fed daily was one of the most sensitive indications of thyroid damage.
6. No thyroid damage was observed in animals receiving 0.15 μ Ci/day (equivalent to a thyroid dose of about 3 rad/wk).

7. One metastasizing fibrosarcoma developed in or immediately adjacent to the thyroid of one ewe that had received $5 \mu\text{Ci}/\text{day}$ since weaning and whose dam had received the same dose during the latter third of the gestation period and all of the lactation period. This was at a level about thirty times the "indifference" level.

The estimated thyroid doses at levels associated with damage are considerably higher than in many other dose-response situations. For example, at $5 \mu\text{Ci}/\text{day}$, where thyroid damage ranged from none to moderate, the calculated doses ranged from 18,000 to 40,000 rad in the thirty-five to fifty-two months of exposure. Even with the uncertainty about what the true weight of the gland was, the levels are all quite high. Ablation doses were over 100,000 rad (with some doubt in the calculation as to how much of the calculated dose was really needed).

Later extensions of the experiments included single intravenous doses, multiple but widely spaced doses, double tracer experiments using ^{125}I and ^{131}I , and a formal comparison of the effect of route of administration. (The difference was less than the variation of uptake between individuals.) Many other aspects were developed, but these fit more conveniently into the problems of fallout and will be discussed in chapter 13. An illustration of the effects on growth is given in figure 8.12.



FIGURE 8.12. Variable growth retardation in three nine-month-old lambs fed $240 \mu\text{Ci}/\text{day}$ with a control animal (on left) of same age. (From Bustad et al. 1957. Reprinted with permission of Academic Press, Inc., Orlando, Florida, copyright 1957.)

3. Miniature Swine

The sheep as a ruminant was not a very good physiological model for extrapolation to humans. Bustad and his colleagues turned to swine for some final iodine work and especially for the new studies with radiostrontium. The pig is an omnivore with dietary requirements and gastrointestinal tract similar to man's. Some early experimental work was actually done at Hanford with the standard porker. But the difficulties and hazards of doing daily experimental work with these enormous and ill-tempered beasts led quickly to the use of miniature swine. First they used Hormel miniature swine, then the Pitman-Moore strain, and for most of the long-term work a cross between the Pitman-Moore and large swine. These have frequently been referred to as "Hanford miniature swine." In addition to the greater ease of handling over the full-sized porker, the miniature swine have a mature weight and organ weights quite comparable to those of man, as well as the similarities in diet and gastrointestinal tract characteristics mentioned earlier. Also, they have a white skin, very useful for studies with topically applied sources.

Some of the characteristics of miniature swine are described by Horstman et al. (1960) and in a symposium (Bustad and McClellan 1966). A special metabolism cage for collection and separation of excreta from these miniature pigs is described in the 1956 annual report (Report HW-47500, 1957). Figure 8.13 is a photograph of a standard porker and the "Hanford miniature swine."

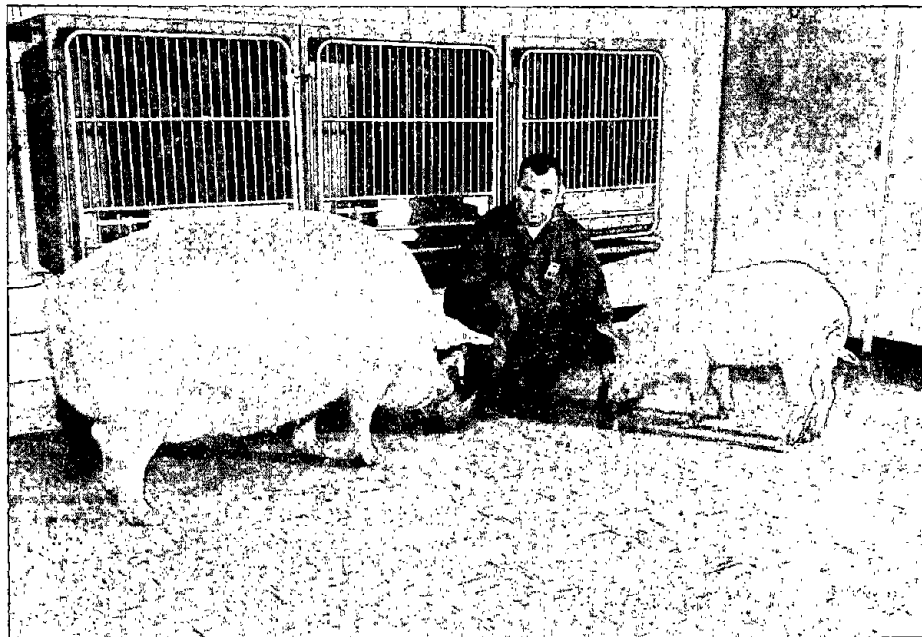


FIGURE 8.13. Comparison of Hanford miniature swine (right) with standard porker. (Courtesy of Pacific Northwest Laboratory.)

Just as the sheep was the anchor species for the iodine work, the miniature swine became the standard large animal at Hanford for major studies with radiostrontium (results described in chapter 13), and for occasional trials with other radioisotopes. The first beagles arrived at Hanford in 1956 for subsequent extensive inhalation studies with plutonium and other transuranics, and the uranium daughter products of importance in uranium mining (chapters 3, 9).

4. Tritium

At almost the same time as the iodine work was started, Roy Thompson, who came to Hanford in 1950, began major studies with tritium. This was also related to Hanford's wartime experiences. Tritium was produced in the reactors as both a fission product and as a result of neutron activation. Also, potentially large releases could occur in the fuel processing operations. The rather considerable production of tritium in the fusion process tied the work nominally to the thermonuclear weapon developments, and the presence onsite of some large sources of tritium, for this project, made the connection much more than nominal. The reports of these experiments appeared in the first annual report (1951) and continued each year until 1955. Early published papers concerned primarily metabolic turnover of tritium as a tracer in rodents (Thompson 1952, 1953, and 1971; and Thompson and Ballou 1954). All of this work showed rapid and complete absorption from the gastrointestinal tract and rapid passage into organs, tissues, and various body fluids. Also, combination with organic moieties was described, and the importance of the ratio between organically bound tritium and free-water tritium to retention times and modes of distribution was pointed out. As Totter remarked at the dedication of the new Life Sciences Laboratory at Richland in 1971, this work (along with studies on man at Los Alamos) constituted some of the earliest definitive experiments on the radiation biology of tritium in mammals.

Small animals were used for most of this work. Elimination by rats and mice showed three half-times, as given by Woodard (1970) from the Hanford and other work as three, ten, and seventy days. These were consistent with the half-times of about eight, twenty, and four hundred days described in man, the slower rate being due to the slower turnover of body constituents in man.

This work, confirmed by a growing crescendo of all types of work with tritium and tritiated water, led to consideration of tritium as one of the least hazardous of the radioactive isotopes. Its low energy poses no danger from external exposure and a very short range for internal exposure. The rapid loss and dilution in body water reinforced this conclusion. But even the early Hanford work indicated that a small amount of tritium acquired as water is incorporated into tissue compounds with retention half-times up to one-third of the life span. Here began a long saga of the importance, or lack of it, of tritium incorporated into key cell constituents—which we shall review in later chapters along with inhalation studies.

5. Radioactive Particles

The "radioactive particle" work was again the result of a local phenomenon—accidental releases, albeit short, of radioruthenium in particulate form from the production plant stacks. There was much concern that these particles, if in the respirable-size range, might act as focal points for lung cancer or, if introduced by other routes, might cause injury out of proportion to the amount of

radioactivity involved. This was one of the origins of the "hot speck" or "hot spot" problem—similar to, but not to be confused with, the hot spot problem in bone. Reports on research with radioactive particles first appear in Hanford annual and other reports in the early 1950s.

6. Plutonium (Except Inhalation)

It is no surprise that biological work with plutonium and other actinides developed in the Biology Department at Hanford. But because of the extensive war work at the Metallurgical Laboratory, at Berkeley, and at Rochester, there was not the pent-up demand for urgently needed data connected with the daily operations of the plant as seen in the case of some of the other work. Reports on plutonium appear in the first annual report. These early reports concerned absorption of plutonium from the gastrointestinal tract and skin as well as treatment for internal plutonium contamination. In addition to the early work pertinent to wound contamination, there was a major effort on the therapeutic removal of these elements, one of the largest and most consistent of the several under way. The work included also gastrointestinal tract absorption, isotopic and chemical differences, behavior and effects in the young and developing animal, and the usual metabolism and effects observations under the various conditions imposed. This work extended to actinides other than plutonium, such as neptunium, americium, californium, and einsteinium, but we will discuss these separately from plutonium.

Of special interest is the rather considerable difference in metabolism of the short-lived isotopes of plutonium compared to the long-lived ^{239}Pu . For example, the shorter-lived ^{238}Pu has a shorter retention time and seems to be more mobile in general. This is quite beyond the difference in radiological half-life and has been attributed, in part, to instability of ^{238}Pu complexes possibly caused by the much greater radiolysis in tissue fluids and in part to the differences in mass.

These phenomena were extended in a study of ^{237}Pu versus ^{239}Pu nitrates in beagle dogs by Bair et al. (1974). Here the specific activity difference is from only about 80 $\mu\text{g}/\mu\text{Ci}$ for the 237 isotope to 16 $\mu\text{g}/\mu\text{Ci}$ for the 239 form. Much more ^{237}Pu was excreted in both urine and feces, much more went to skeleton and much less to liver. These differences are consistent with the idea that much more of the 237 isotope is in the monomeric form, while much more of the heavier form is in polymeric form (i.e., a radiocolloid). The difference lasted over at least thirty days and is, thus, far from a transient phenomenon.

Another example of the Hanford nonrespiratory studies is work on the combined toxic effects of plutonium plus x ray (Ballou, George, and Thompson 1962). The x rays did not change distribution or excretion of the plutonium, but the lethal effect of either x ray or plutonium is markedly increased in rats by their combined application.

It was logical to include plutonium in the work with swine. This was done by Leo Bustad and colleagues with the first published paper appearing in the proceedings of the first Hanford biology symposium held in May 1962. Naturally the work extended back over ten to a dozen years. The 1962 report (Bustad et al. 1962) gives the major objectives of the study as metabolism by various routes of administration, toxicity of plutonium compared to some other bone seekers in the pig, effects on skin and removal therefrom of plutonium injected or topically applied. (Again the motivation was from the practical problems of plutonium in wounds.) The routes of entry were intravenous, intragastric, and

intratracheal. The element was given as the valence IV nitrate. Liver contained more plutonium than bone by all routes and at all times from as short as 11 days to as long as 695 days. But the concentration ratio was much higher after intravenous than after intratracheal or intragastric administration. The fraction of administered dose reaching these organs was, of course, much lower after entry via lung or gut. This behavior is quite comparable to that seen in other species and is consistent with the idea that the intravenous route evidences much more radiocolloid formation than when the element is absorbed through gut or lung wall. The effects work reported was very preliminary but included reporting of a 40% reduction in blood neutrophil count after one-half to one year at $1.3 \mu\text{Ci } ^{239}\text{Pu/kg}$ body weight given by vein. There were also early changes in bone. There is no mention of tumor development.

A companion study by Clarke (1962) takes up the histopathology in bone in more detail and provides one of the few comparisons of plutonium with strontium and radium in the pig. Injections were made at one, five, six, or twelve months of age. There were differences in details of the damage produced consistent with the deposition of plutonium as a surface seeker and strontium and radium as volume seekers. Plutonium was consistently more damaging than ^{90}Sr or ^{226}Ra , but since the results were not amenable to quantitation, no toxicity ratio calculations were attempted. The effects in pig bone were, in general, quite comparable to those seen in the Utah intravenous studies with beagle dogs, except that the experiment did not reveal bone tumor development.

The intradermally injected plutonium was reported upon by Cable et al. (1962). There was appreciable, but not large, absorption from the injection site, with about 12% of the injected dose appearing in regional lymph nodes; about 7% in liver, and about 5% in bone. (The plutonium was injected as the nitrate.) Ulcers formed at the injection site at the highest dose, $5 \mu\text{Ci}$ of ^{239}Pu , but histopathological analysis showed changes in skin structures at lower concentrations.

This symposium saw also many reports on the other actinide elements, americium, neptunium, and californium, some of them from the Hanford group. These will be taken up as part of the general review of the transplutonic elements in section VI of this chapter.

7. Gastrointestinal Tract

The Hanford operation housed what is probably the most intensive attack in U.S. work on both radiation injury to the gastrointestinal tract and the absorption of a large number of radionuclides from the gastrointestinal tract.

It started with the early studies of Katz, Kornberg, and Parker (1955) on the absorption of plutonium from the gastrointestinal tract of rats and extension of the work to swine by Weeks et al. (1956). They confirmed in an animal with a gastrointestinal tract more closely resembling man than the rodents used earlier that normally plutonium is very poorly absorbed.

When Maurice F. Sullivan arrived at Hanford in 1955, studies began that are still being continued. In the earlier phases, the group was interested primarily in radiation injury from both external radiation sources and from radioisotopes passing through the gastrointestinal tract, the latter, in part, a result of the radioactive particle problem mentioned earlier. Much of this work, along with contemporary studies elsewhere, was contained in the sixth Hanford biology symposium (Sullivan 1968). This emphasized effects and reflected the general interest in the gastrointestinal tract syndrome then current.

As interest focused more on low levels of radiation exposure, the possible effects of small amounts of radioisotopes passing through the tract and their metabolic behavior became dominant in the work. The latter grew to be paramount as it became apparent that effects at low levels were not going to be detectable in the gastrointestinal tract. This was stimulated by the need for good figures on gastrointestinal tract absorption for the setting of intake limits for the over two hundred radioisotopes in the 1959 ICRP-NCRP recommendations for maximum permissible concentrations. Also, the fact that the gastrointestinal tract came up as a critical organ in a surprising number of cases helped to change the focus of interest.

One of the very early findings of significance, the poor absorption of plutonium in the +4 valence state from the gut, seen in Hamilton's work with the rat, was amply confirmed, as was the tendency for plutonium entering in other valence states to be converted to the +4 state. The greater absorption of ^{238}Pu and of several of the transplutonics was also made clear. Recently (Sullivan 1980), absorption of ^{228}Th , ^{232}U , ^{237}P , ^{237}Pu , ^{238}Pu , ^{239}Pu , ^{241}Pu , ^{241}Am , ^{244}Cm , ^{252}Cf , and ^{253}Es from the gastrointestinal tract was measured in neonatal rats, guinea pigs, and swine receiving the nuclides in solution or suspension by gavage. While particle size, valence state, chemical form, and age of the animal all had their effect, the absorption by newborn was uniformly twenty (swine) to one hundred (rats) times that seen in the adult. Such findings have been quite general and are not limited to the actinides. They have led to the introduction of special considerations for oral intakes by the very young.

Two basic problems have come into focus around this work at Hanford and contemporary work elsewhere. The first concerns the validity of the gavage technique for administering radioisotopes, or indeed any substance, for measurement of gastrointestinal tract uptake. The practice has been to starve the animal prior to administration to avoid combination of the radioelement with the contents of the gastrointestinal tract. This was true in the earlier Hanford work. In fact, the animals were frequently starved for a period *after* gavage for the same reason. Sullivan (1979) emphasized the fact that, when given by gavage to a starved animal, hexavalent plutonium is absorbed to almost one thousand times the extent of tetravalent plutonium. But if food is present in the gut, the hexavalent state is very short-lived, and conversion to the +4 state occurs rapidly, and absorption is considerably reduced. Thus, in his view, the higher absorption figure of the +6 state is of no practical significance in normal exposures where there is almost sure to be some food in the gastrointestinal tract. (a) These findings do not seem to apply to all elements, probably because of differences in their chemical behavior within the milieu of the gastrointestinal tract.

As a result of findings such as these at Hanford, there is now a strong tendency to administer isotopes for determining gastrointestinal tract uptake to recipients in as near a normal nutritive state as possible. The large sheep and swine experiments used this mode even in the early days, as did the beagle project at Davis. But there is much yet to learn about how much difference the presence of food makes. It seems to be isotope-specific and a subject for still further research by groups like the one at Hanford.

(a) Experiments at other laboratories, e.g., Rochester, put the animal back on regular feed immediately after gavage. It is not proven how much, if any, effect this may have on the derived figure for absorption. But this difference in practice might account for some of the variability of results seen in the literature.

The second problem of the gavage technique is the concentration of isotope and its availability rate. In the original type of gavage experiment, a considerable slug of material arrived all at one time. Some of the work using feeding techniques indicates that fractional absorption may be greater when the concentrations are low. This again appears to be true of some elements and not of others.

The Hanford people approached another facet of these problems, in part, by using different isotopes of plutonium, which because of their wide range of half-lives covered a considerable range of specific activities. Here the total mass associated with a given activity could be varied significantly. Other things being equal, the activity entering the body from a small mass was more mobile in most respects, including gastrointestinal tract absorption.

Another facet under current study provides reasons to suspect that passage through the food chain may render some elements more transportable in general, so that gastrointestinal tract absorption is higher than from a freshly mixed solution or a freshly prepared pellet of feed. A typical example of the Hanford approach to this phenomenon is seen in a paper by Sullivan et al. (1980) in which rats and guinea pigs were given alfalfa containing ^{239}Pu . Differences in absorption of up to a factor of five occurred when the plutonium was mixed with alfalfa leaves and up to a factor of ten when the plutonium was accumulated by alfalfa leaves by growth in contaminated soil. We will return to these problems when we consider environmental pathways in chapter 15.

8. Studies with the Fetal and Juvenile Mammal

We frequently hear complaints that not enough is known about the effect of age, particularly very young ages, on the behavior and effects of radioisotopes entering the body. This becomes, of course, of particular importance as the process of standard-setting shifts from occupational to population exposures. The complaint is true to a degree, but it rests more on the complexity of the problem than on simple lack of pertinent research. The Hanford group has been a major contributor to the storehouse of information we do have. While some of the studies occurred relatively early, the development of a consistent and concentrated attack dates from the arrival of Melvin Sikov at Hanford in 1965. Sikov became interested in the general problems of the effect of toxic agents, particularly radiation and radioisotopes, early in his research career (Sikov 1979). He has stayed close to the field ever since with his colleague of many years, D. D. Mahlum.

The effect of age on sensitivity to, and effects from, external radiation sources has been well established. With internally deposited radioisotopes, the problems are much more complex. Age influences absorption and distribution. As the organism grows, the size and weight of the organs change so the concentration of nuclide changes, even if the actual amount present remains relatively constant. Each element has its individual pattern, indeed different chemical forms of the same element have their individual behavior.

An informative illustration of these phenomena is found in a paper by Mahlum and Sikov (1974). The abstract of this paper tells the story and is reproduced below:

Newborn (0-24 hr. old), weanling (21 days old), and adult (4 mo. old) rats were injected intravenously with doses of monomeric or polymeric ^{239}Pu over the range of 6-90 $\mu\text{Ci/kg}$. Some animals from each age-dose-form group were killed at intervals for determination of distribution and retention while the remaining rats were

held for observation of acute mortality and several measures of delayed change. The most notable difference in partition involved a failure of the newborns to differentiate between the two physicochemical forms and an increased skeletal deposition in the weanlings exposed to monomer. As a result of these differences in deposition, as well as differences in retention and dilution, the cumulative radiation doses differed for the three ages. On an injected dose basis, monomeric ^{239}Pu was more acutely toxic to newborn rats, $\text{LD}_{50/30} = 63 \mu\text{Ci/kg}$, than to adult or weanling rats, $\text{LD}_{50/30} = 90 \mu\text{Ci/kg}$. Polymeric ^{239}Pu was more acutely toxic to adult and weanling rats, $\text{LD}_{50/30} = 47 \mu\text{Ci/kg}$, than to newborn rats, $\text{LD}_{50/30} = 77 \mu\text{Ci/kg}$. Delayed deaths, between 90 and 270 days after injection, were more frequent among adults injected with monomeric ^{239}Pu at levels of 6-90 $\mu\text{Ci/kg}$ (14/41, 90-day survivors) or among either weanling or newborn rats given either form of ^{239}Pu . Delayed effects such as mortality and mammary tumor incidence appeared to be influenced by the pattern of radiation doses associated with the physicochemical form administered and the age at exposure. (Mahlum and Sikov 1974)

A succinct summary is given by Sikov and Mahlum (1972) in which influences of age on absorption, partition, critical organ, and radiation sensitivity and the role of differential organ growth are each taken up.

Probably the earliest comprehensive study, from Hanford, of the absorption of plutonium relative to age is the one by Ballou (1958).

We can trace back the evolution of this facet of the work at Hanford by following it in the annual biology research reports.

In the report for 1961 (HW-72500, January 1962), we find:

Effect of Age on Retention of Strontium and Calcium. R. O. McClellan, A. C. Case, and H. W. Casey.

By the 1966 report (BNWL-480, July 1967), we find:

Effect of Age on Absorption of Plutonium from the Gastrointestinal Tract of Rats. D. D. Mahlum and M. R. Sikov.

Cross-Placental Passage of Actinides in the Rat. M. R. Sikov and D. D. Mahlum.

Neptunium-Induced Fatty Livers in Rats: Electron Microscopic and Biochemical Studies. J. D. Berlin and D. D. Mahlum.

Distribution of Cerium-144 in the Fetal and Newborn Rat. D. D. Mahlum and M. R. Sikov.

Age-Related Differences in the Metabolism of Cesium-137 by the Rat. D. D. Mahlum and M. R. Sikov.

Interrelationships Between Environmental Temperature and Diet in the Distribution and Retention of Cesium-137 in the Rat. D. D. Mahlum and M. R. Sikov.

Age Dependence of Radioiodine Metabolism and Effect in Rats. M. R. Sikov.

By the time of the 1971 report (BNWL-1650, Pt. 1, September 1972), a whole section is set aside and labeled as below:

Metabolism and Effects of Radionuclides in the Developing Fetus and the Young

The Carcinogenicity of ^{131}I Relative to Age at Exposure. M. R. Sikov, D. D. Mahlum, and W. J. Clarke.

Influence of Age on the Late Effects of Monomeric ^{239}Pu in the Rat. D. D. Mahlum and M. R. Sikov.

Plutonium and the Liver of the Immature Rat. M. Kashima, D. D. Mahlum, and M. R. Sikov.

Distribution and Subacute Toxicity of ^{253}Es in Weanling and Adult Rats. D. D. Mahlum, M. R. Sikov, and M. Kashima.

Distribution of ^{253}Es in the Fetoplacental Unit of the Rat. M. R. Sikov and D. D. Mahlum.

^{253}Es and ^{249}Bk Distribution in Rat Tissues Following Intragastric and Intravenous Administration. F. P. Hungate and D. W. Baxter.

The report for 1973 (BNWL-1850, Pt. 1, August 1974) carries the following pertinent papers:

Plutonium Metabolism in the Lactating Rat. D. D. Mahlum and M. R. Sikov.

Plutonium Metabolism in Immature Swine. B. J. McClanahan, H. A. Ragan, and D. D. Mahlum.

Cross Placental Studies with ^{238}Pu . M. R. Sikov, M. Dedrick, and D. D. Mahlum.

Effects on the Rat Embryo of Combined Exposure to ^{239}Pu and Trypan Blue. M. R. Sikov and D. D. Mahlum.

Effects of ^{253}Es in Weanling and Adult Rats. D. D. Mahlum, M. R. Sikov, and F. P. Hungate.

For 1974 (BNWL-1950, Pt. 1, March 1975), the material is again gathered together under a common heading:

Toxicology of Radionuclides in the Fetal and Juvenile Mammal

Influence of Age on the Development of Bone Tumors in Rats Injected with ^{239}Pu Citrate. D. D. Mahlum and M. R. Sikov.

Metabolism of ^{241}Am Citrate in Rats Relative to Age. D. D. Mahlum and M. R. Sikov.

The Toxicity and Distribution of ^{241}Am and ^{244}Cm in the Rat After Administration at Nine Days of Gestation. M. R. Sikov and D. D. Mahlum.

Effects of ^{253}Es Injected in Weanling and Adult Rats. D. D. Mahlum, M. R. Sikov, and F. P. Hungate.

Effect of Irradiation on the Development of Fetal Rat Lung in Organ Culture and in Utero. J. C. Vogt, M. R. Sikov, and D. D. Mahlum.

These listings should be enough to give both the extent and the depth of the effort concerning fetal and juvenile animals.

A Hanford biology symposium (Sikov and Mahlum 1969) brought together an international group interested in both radionuclides and external radiation effects. The published proceedings provided, in a single volume, a quite complete summary of the status of the world's literature at that time, and several papers were derived from the work reported earlier in the annual progress reports.

The greater radiosensitivity of growing tissues and organs and the key periods of special sensitivity during embryogenesis seen with external radiation sources were confirmed in the radionuclide work, but the complexities of isotope metabolism and dosimetry make generalizations difficult. In general, the work showed more rapid adsorption and greater mobility for the radioelements in very young and embryonic animals and critical dependence of effects on the stage of development. Also, in general, the differences as compared to the adult began to decrease at the time of weaning.

9. Therapy

In the discussion of radium and polonium, we reviewed some of the attempts to influence deposition or hasten removal by changes in diet or the use of various specific therapies. As we shall see in the consideration of research stimulated by the problems of fallout from weapons testing, similar ideas were applied to the fission products, especially radiostrontium.

As Thompson (1956) remarked, Hanford was a very likely place for interest in the therapeutic removal of plutonium. The possibilities of worker contamination were always nearby, and both the research and medical operations felt the immediacy of being prepared with possible therapy. Indeed, in his paper, Thompson gives a tabulation of one hundred plutonium deposition cases over a ten-year period, albeit only one thought to be above the maximum permissible level, and only three above 20% of same.

W. D. ("Dag") Norwood, the quietly competent physician who had had as his responsibility the health of thousands of construction workers who had built Hanford, and later all of the local General Electric employees, reviewed at the same Argonne conference (Norwood 1956) some of the clinical considerations surrounding therapeutic removal of elements like plutonium. Both Thompson and Norwood discuss and compare the efficacy of one of the quite early agents, zirconium citrate (whose saga we shall review in a general consideration of therapeutic measures), with one of the moderately early chelating agents, Ca-EDTA (see chapter 19). Thompson cites two papers (Katz, Kornberg, and Parker 1955; Weeks et al. 1956) and reports from the *Hanford Annual Report* for 1953. Thus, there was significant early interest and activity at Hanford relating to the therapeutic removal of deposited radionuclides. Considerable interest had persisted at Chicago and Berkeley and had grown at Los Alamos. Also, the new laboratories at Utah and Lovelace Foundation joined the effort. The big question, as we shall see later, was toxicity of the therapeutic agent.

At Hanford, one of the more sustained efforts in chelation therapy began when Dr. Victor Smith, a chemist who had come to Hanford in 1954 and worked on the ruthenium particle and plutonium inhalation exposures for a couple of years, transferred to Roy Thompson's section and became intrigued with chelation chemistry. Although many coauthors came and went, Smith could be depended upon for items pertinent to therapeutic removal in the annual reports and journal publications. This was still going on at the end of the period covered by this book. Examples are Ballou et al. (1977); Sikov, Smith, and Mahlum (1975); and sections in the annual reports for 1976 and 1977.

Discussion of the results will be held for the general review of therapy in chapter 19, except to remark on a few items of special pertinence to the Hanford setting (Smith 1979). Along with Chicago and Los Alamos workers, and studies abroad, they found the chelating agent DTPA much superior to EDTA in

removing injected plutonium citrate in rats. Norwood gave it very early trials in man in a dose of 1 g (because that was the size ampule it was packaged in).

Later, to avoid the clumsy intravenous drip administration, DTPA was placed in a small nebulizer so that it could be inhaled. Besides greater convenience, this might be especially effective for an inhalation exposure. But some questions were raised when animals receiving up to ten times the likely human dose of these aerosols showed what was termed a "transient emphysema" (Ballou via Smith 1979). Further Hanford work, and particularly extensive experience in France, makes it appear that this may have been an isolated observation, however.

Nevertheless, the key problem remains the toxicity of the therapeutic agent—and there have been some doleful incidents (not at Hanford) to underline these reservations.

10. Symposia and Other Special Publications

a. Life Sciences Symposia

Beginning in 1962, the Hanford Biology Operation and its successor Pacific Northwest Laboratory sponsored annual symposia on subjects bearing on their research programs. These were not anniversary volumes, as in the case of the Utah symposia, and they cover a wider range of subjects. But a significant number brought together work and workers in the field of radioisotope toxicology. Like the Utah symposia, they provided many opportunities for review of local work, as well as national and international research. The symposia became more and more international, as did the reputation of the Laboratory, and many a delegate from the closely coupled countries of Europe had his first chance to appreciate why the Manhattan Engineer District chose this vast, still somewhat isolated site, to locate the plutonium production reactors.

A list of the Hanford symposia and their proceedings follows:

First Symposium—The Biology of the Transuranic Elements. 28-30 May, 1962, R. C. Thompson, ed. *Health Phys.* 8(6):561-780, 1962.

Second Symposium—The Biology of Radioiodine. 17-19 June, 1963, L. K. Bustad, ed. *Health Phys.* 9(12):1081-1426, 1963.

Third Symposium—Inhaled Radioactive Particles and Gases. 4-6 May, 1964, W. J. Bair, ed. *Health Phys.* 10(12):861-1259, 1965. Also published as hard-cover book by Pergamon Press.

Fourth Symposium—Radiation and Terrestrial Ecosystems. 3-5 May, 1965, F. P. Hungate, ed. *Health Phys.* 11(12):1255-1675, 1965.

Fifth Symposium—Swine in Biomedical Research. 19-22 July, 1965, L. K. Bustad and R. O. McClellan, eds. USAEC and Battelle Memorial Institute, 834 pp., 1966.

Sixth Symposium—Gastrointestinal Radiation Injury. 25-28 September, 1966, M. F. Sullivan, ed. Excerpta Medica Foundation, 542 pp., 1968.

Seventh Symposium—Diagnosis and Treatment of Deposited Radionuclides. 15-17 May, 1967, H. A. Kornberg and W. D. Norwood, eds. Excerpta Medica Foundation, Monographs on Nuclear Medicine and Biology No. 2, 681 pp., 1968.

Eighth Symposium—Myeloproliferative Disorders of Animals and Man. 20-23 May, 1968, W. J. Clarke, E. B. Howard, and P. L. Hackett, eds. USAEC Office of Technical Information Services. CONF-680529, 765 pp., 1970.

Ninth Symposium—Radiation Biology of the Fetal and Juvenile Mammal. 5-8 May, 1969, M. R. Sikov and D. D. Mahlum, eds. Div. Technical Information, USAEC CONF-690501, 1026 pp., 1969.

Tenth Symposium—Pollution and Lung Biochemistry. 2-5 June, 1970, D. B. Menzel, ed. Archives of Internal Medicine Symposia, Vol. 9, 282 pp., 1971.

Eleventh Symposium—The Biological Implications of the Transuranium Elements. 27-29 September, 1971, R. C. Thompson and W. J. Bair, eds. *Health Phys.* 22(6):533-954, 1972.

Twelfth Symposium—Radionuclide Carcinogenesis. 10-12 May, 1972. C. L. Sanders, R. H. Busch, J. E. Ballou, and D. D. Mahlum, eds. USAEC Office of Information Services, CONF-720505, 500 pp., 1973.

Thirteenth Symposium—The Cell Cycle in Malignancy and Immunity. 1-3 October, 1973, J. C. Hampton, ed. U.S. Energy Research and Development Administration, Office of Technical Information Services, CONF-731005, 605 pp., 1975.

Fourteenth Symposium—Radiation and the Lymphatic System. 30 September-2 October, 1974. J. E. Ballou, ed. U.S. Energy Research and Development Administration, Technical Information Center, CONF-740930, 258 pp., 1976.

Fifteenth Symposium—Biological Implications of Metals in the Environment. 29 September-1 October, 1975. H. Drucker and R. E. Wildung, eds. U.S. Energy Research and Development Administration, Technical Information Center CONF-750929, 682 pp., 1977. (Note: Only a few of the papers concern radioisotope metabolism.)

Sixteenth Symposium—Pulmonary Macrophage and Epithelial Cells. 27-29 September, 1976. C. L. Sanders, R. P. Schneider, G. E. Dagle, and H. A. Ragan, eds. U.S. Energy Research and Development Administration, Technical Information Center CONF-760927, 618 pp., 1977.

Seventeenth Symposium—Developmental Toxicology of Energy-Related Pollutants. 17-19 October, 1977. D. D. Mahlum, M. R. Sikov, P. L. Hackett, and F. D. Andrew, eds. U.S. Department of Energy, Technical Information Center, CONF-771017, 646 pp., 1978.

Eighteenth Symposium—Biological Effects of Extremely Low Frequency Electromagnetic Fields. 16-18 October, 1978, R. D. Phillips, M. F. Gillis, W. T. Kaune, and D. D. Mahlum, eds. U.S. Department of Energy, Technical Information Center, CONF-781016, 577 pp., 1979.

Nineteenth Symposium—Pulmonary Toxicology of Respirable Particles. 22-24 October, 1979. C. L. Sanders, F. T. Cross, G. E. Dagle, and J. A. Mahaffey, eds. U.S. Department of Energy, Technical Information Center CONF-791002, 676 pp., 1980.

Twentieth Symposium—Coal Conversion and the Environment: Chemical, Biomedical, and Ecological Considerations. 19-23 October, 1980, D. D. Mahlum, R. H. Gray, and W. D. Felix, eds. U.S. Department of Energy, Technical Information Center, CONF-801039, 607 pp., 1981.

Twenty-First Symposium—Biological Availability of Trace Metals. 4-8 October, 1981, E. A. Jenne and R. E. Wildung, eds. *Sci. Tot. Environ.* (special issue) 28:1-519, 1983.

Twenty-Second Symposium—Life-Span Radiation Effects Studies in Animals: What Can They Tell Us? 27-29 September, 1983, R. C. Thompson and J. A. Mahaffey, eds. U.S. Department of Energy, Technical Information Center, CONF-830951 (DE83016860), 1986.

Twenty-Third Symposium—Interaction of Biological Systems with Static and ELF Electric and Magnetic Fields. 2-4 October, 1984, L. E. Anderson, B. J. Kelman, and R. J. Weigel, eds. Pacific Northwest Laboratory, CONF-841041, 1987.

Twenty-Fourth Symposium—Health and Environmental Research on Complex Organic Mixtures. 20-24 October, 1985, R. H. Gray, E. K. Chess, P. J. Mellinger, R. G. Riley, and D. L. Springer, eds., Pacific Northwest Laboratory, CONF-851027, 1987.

Twenty-Fifth Symposium—Radiation Protection—A Look to the Future. 21-23 October, 1986, W. J. Bair, ed. *Health Phys.* (special issue).

Twenty-Sixth Symposium—Modeling for Scaling to Man: Biology, Dosimetry, and Response. 20-23 October, 1987, J. A. Mahaffey and J. A. Mewhinney, eds. *Health Phys.* (supplement).

b. Others

In addition to the yearly symposia, the Hanford people have, of course, organized and contributed to many other documents of interest to anyone tracing the development of internal emitter toxicology over the years.

A very early compilation was an "Official Use Only" report entitled *Plutonium Metabolism, A Literature Review* by J. Katz of the then-new Biology Division of the Health Instruments Division (Katz 1951). This contains tabular and descriptive summaries of the early work. The section headings herald most of the basic problems that have occupied our attention ever since. Fifty-eight references served to cover the highlights in those days!

A comprehensive review and commentary called "Biological Factors" for the handling of plutonium was prepared by Roy Thompson for the much-used "Plutonium Handbook," edited by O. J. Wick (Thompson 1967). In addition to over two hundred references, this chapter has very useful summary tables.

A volume with similar objectives was compiled by Roy Thompson and published in 1973 as a bibliography of the transuranium elements (Thompson 1973). This includes over one thousand literature citations. Three years later, a new edition contained sixteen hundred references, carefully selected (Thompson 1976).

Important compendia involving Hanford initiatives and/or participation bear especially on inhalation toxicology problems, as we shall see in chapter 9. We should add to these the lengthy summary-type documents prepared as testimony for the many hearings held by U.S. government agencies in the mid-1970s. These will be examined in due course, along with the roles played by the several large laboratories like Hanford in helping the Congress and the executive branches go through the agonizing process of trying to determine what is really known and what yet needs to be done after all the years of work and interpretations.

In the period from 1948 to the present, Hanford and its successor organization, PNL, has become one of America's prime centers for biological research involving radioisotope toxicology, both basic and applied.

B. Los Alamos Scientific Laboratory

1. Transition

During the years of World War II, there was no intention that the Los Alamos Laboratory would become a permanent installation. The single objective was developing an atomic weapon at the earliest possible moment.

In 1945–1946 many key personnel in physics and chemistry, including the wartime director, Robert Oppenheimer, departed. The buildings were of temporary-type construction and some of them fearfully contaminated. They would need either major reconstruction or replacement. Spirits were very low. Yet, the spark for continuation and extension was there. Thanks largely to Norris Bradbury who replaced Oppenheimer as director, Wright Langham who headed the health research, Ernest Anderson, and a few others, a viable core of dedicated personnel provided the basis for a comparative renaissance in 1946–1947 (Shipman 1969).

We saw in chapter 7 that Los Alamos was allowed to do very little biomedical research during the war, only work connected with the medical care of the workers (Hempelmann) and some studies of plutonium excretion in animals and man for purposes of bioassay (Langham). Oppenheimer was against having any biomedical research at Los Alamos. Let Chicago, Berkeley, Rochester, et al. provide that. Even the study of plutonium metabolism in patients, sparked by Los Alamos, had to be carried out elsewhere. Hempelmann and Langham had to fight hard to get whatever support they could during the war years. The size of the research operation can be judged by the size of the building that housed the Health Group in 1945. This structure is shown in figure 8.14A. Also shown is the building in which much of the plutonium chemistry and metallurgy was done (figure 8.14B). Realize that this was an improvement over the earlier facilities!

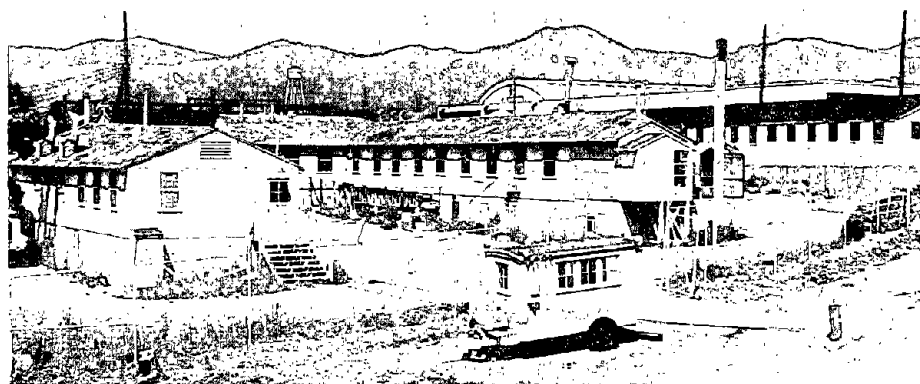


FIGURE 8.14A. View of the early biology facilities at Los Alamos commonly referred to as the "Rat House" or "Rat Lab." The wartime facility was smaller yet. (Photo courtesy of Dr. George Voelz, Los Alamos.)

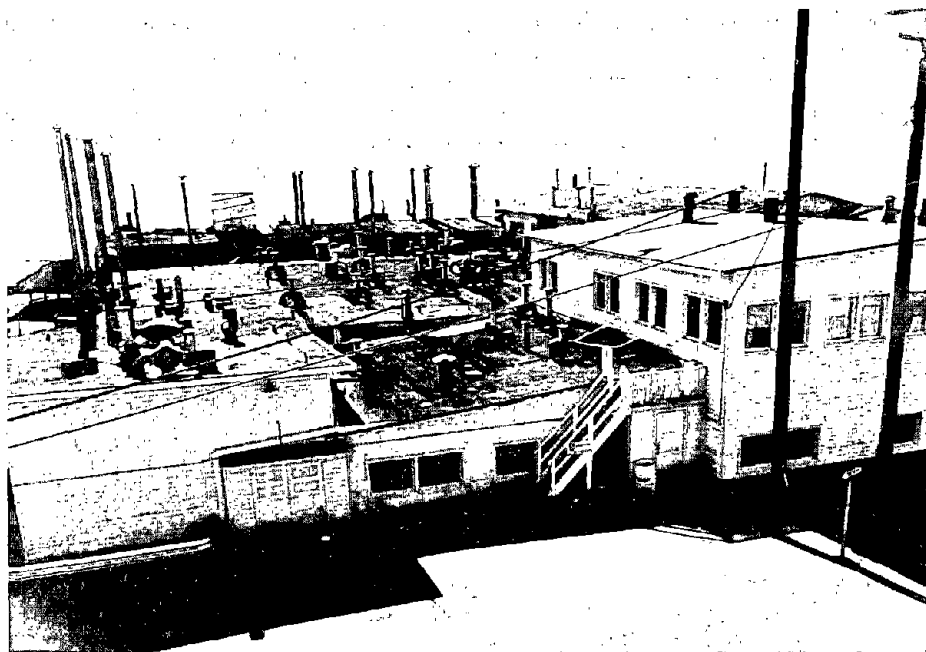


FIGURE 8.14B. View of the “D” Building at Los Alamos in which much of the plutonium metallurgy and chemistry were done. Note that only some of the exhaust stacks are suitably far above the roof line. (Photo courtesy of Dr. George Voelz, Los Alamos.)

In the genesis of the Utah beagle experiment, the keen interest of the Los Alamos staff in getting much more information on plutonium toxicology was amply demonstrated. Even though Los Alamos was not the place for a king-sized dog experiment, there were many things the laboratory could do in the health sciences if the support were given. After a devastating review of safety at Los Alamos, particularly regarding ventilation, waste disposal, etc., by the newly created Safety and Industrial Health Advisory Board of the new AEC, the decision had to be made whether to go on and build up or scrub the operation. It was apparent to many at the time that the nation's security required continuation of a development laboratory like Los Alamos. The decision was made to build up. The so-called H-Division was created to include the former medical surveillance operation, more industrial hygiene and health physics, and related research. Advice regarding health and safety problems was sought from Philip Drinker at Harvard. Harriet Hardy, who had trained with Alice Hamilton,^(a) was loaned to Los Alamos in 1948 by the Massachusetts Division of Occupational Hygiene. Their influence brought Harry Schulte in to start a real industrial hygiene program. Tom Shipman was appointed as overall medical director in 1948. Harry Whipple had responsibility for the medical group. Wright Langham had the Biomedical Research Group and widespread interests and foresight.

(a) The legendary advocate for worker safety and a pioneer in occupational health.

Biomedical research expanded from plutonium to related elements such as americium (Shipman 1969). In the biochemistry group, some of the first syntheses of ^{14}C into biologically important molecules were accomplished.

With the program under way for real, a commodious Health Research Laboratory was constructed in 1952, followed in 1960 by an annexed animal facility. In general, the laboratory stuck to small animals and man insofar as internal emitter toxicology research was concerned. Through the foresight of Langham and Hempelmann, a nucleus of the wartime workers was earmarked for a prospective study of amounts of plutonium present and possible effects (more in chapter 16). Quite sizeable groups were also gradually developed in molecular and cellular radiation biology using primarily enzyme systems, cells in tissue culture, and microorganisms. The Health Division added considerable work in mammalian radiobiology using external radiation sources, included dogs and monkeys on occasion, plus an isotope application section. In later years, an environmental studies section was formed. Much thinking was done about approaches to the problems of inhalation toxicology, even though Los Alamos avoided the generation of aerosols by using microspheres bearing plutonium, as we shall see in chapter 9.

The H-Group numbered 125 in 1951–1952. By 1969, there were 260 personnel aboard. There was not a proportionate increase in the internal emitter research group. They made up for that, however, by having many of the most experienced and most dedicated personnel. What work was done with internal emitters was of very high quality. Some of that which is most germane to the subject of this chapter is reviewed in the following sections.

2. Actinide Research

While relatively small compared to the programs at Chicago, Utah, and Hanford, the Los Alamos work in the actinide field had a special quality. The medical follow-up of some of the Los Alamos plutonium workers has provided landmark information. Dr. Louis Hempelmann, who had been responsible medically for those workers during the war, continued as a central figure in this work, even though he had by then gone to the University of Rochester. Wright Langham and the medical group analyzed autopsy tissue for plutonium from the worker group. This included a victim of a criticality excursion who had been exposed over several years to plutonium aerosols (Foreman, Moss, and Langham 1960). The Los Alamos experience was written up in useful review papers such as those by Langham (1959) and Langham et al. (1962). Ten years later, a similar review encompassed several of the transuranium elements (Langham 1972).

In a more experimental vein, Langham and his colleagues published on the metabolism of plutonium in the rat, and Harry Foreman published a large number of Los Alamos reports and journal papers on therapeutic removal of plutonium from its deposition sites in bone.^(a) Included was a discussion of the mechanism of plutonium uptake by bone (Foreman 1962).

Langham, of course, continued his work on the kinetics of plutonium excretion with papers in the 1950s and 1960s (e.g., Langham 1957, 1964), which built upon the work described in chapter 7. A considerable polemic grew up around the virtues and defects of some rather small differences in formulation of

(a) All of the work on therapy will be considered separately in chapter 19 devoted to that subject.

excretion kinetics (Parker 1973). Some of the problem resides in the high variability of daily excretion rates (Snyder, Ford, and Warner 1968). While still at Hanford, Healy produced a classic paper (1957) on estimation of plutonium lung burden by urine analysis, a step beyond the estimation of body burden.

Since much of the nuclear weapons testing activity was generated at Los Alamos, it is not surprising that members of the H-Group became deeply involved with the biomedical implications of the tests. This included a very effective crusade by Langham on the implications of local area contamination with plutonium in the event of a nonnuclear detonation. Healy became interested in the movement of plutonium in soils and the problems of residual contamination, not only at the test sites in the continental United States and in the Pacific, but around industrial plants such as the one at Rocky Flats near Denver.^(a)

The Los Alamos staff also participated in depth in the Energy Research and Development Administration (ERDA) and the Environmental Protection Agency (EPA) hearings on the Liquid Metal Fast Breeder Reactor plans and other aspects of the so-called plutonium economy. As part of this, concern arose regarding possible genetic changes that might be induced by deposition of plutonium in gonadal tissues. This led to a valuable summary of most of the available information by Richmond and Thomas (1975) prepared just before Richmond left Los Alamos for Oak Ridge. This paper shows how minute is the concentration of plutonium and other actinides in gonadal tissue. Its abstract is given below:

This report summarizes available information on the gonadal content of mammalian species given various actinide elements by various routes of administration. Emphasis is placed on plutonium. Also discussed is the contemporary level of plutonium from nuclear weapons fallout in human subjects. The fraction of the administered burden of plutonium found in the gonads (FABG) of five mammalian species following intravenous injection was about 3×10^{-4} with only about a factor of 10 between the highest and lowest values to allow for differences between sexes, among species or as a function of time following injection. FABG values tend to be smaller in the female, as compared with the male, and following inhalation or subcutaneous implant. Data on the FABG for other actinides are qualitatively similar to those for plutonium. The gonadal plutonium concentrations from fallout in U.S. residents are about 0.5 pCi/kg, not unlike those reported for other soft tissues, except thoracic lymph nodes, and bone. (Richmond and Thomas 1975)

As part of a general attack on the biological response to small, discrete, highly radioactive sources, Richmond et al. (1968) fed 0.5 Ci of $^{238}\text{PuO}_2$ to beagles for six months. This was responsive to some of the concerns surrounding high-specific-activity heat sources for thermoelectric generators and also pertinent to the "hot particle" problem (cf. chapter 9). The effects on the gastrointestinal tract were relatively minor, although not zero. This agreed with findings at Hanford. An astonishingly large amount of insoluble alpha-particle-emitting radioactive material can pass through the gastrointestinal tract with little damage, either structural or functional. Work with rat lung was reported by Richmond, Langham, and Stone (1970). (More in chapter 9.)

In 1974, the Los Alamos group sponsored a major symposium on actinide research (Healy 1975). Much of it was aimed at problems of plutonium in man and problems of standard-setting generated by ferment regarding plutonium

(a) We will review the problems of nonnuclear detonations and general area contamination with plutonium in chapter 14, and general problems of isotope transfer in the environment in chapter 15.

standards developed in the hearings on breeder reactors. A typical example of the subject matter can be found in a paper by Stannard (1975a). The Los Alamos contributions, besides the planning and hosting, were, as usual, quite directly concerned with the applied problems.

3. Tritium

The Los Alamos contributions to tritium research were much like those from Hanford, i.e., more or less directly connected with daily problems in the work of the laboratory, including the development of fission-fusion weapons. While much of the work with tritium concerns environmental distribution and effects, or its embodiment into cells and biomolecules, an early Los Alamos study went directly to its metabolism in man. An Air Force officer, Dr. E. A. Pinson, was assigned in 1950-1952 to Los Alamos primarily to help with some biomedical aspects of the nuclear weapons testing program. But he found time to join with Wright Langham in some definitive laboratory research. Not by coincidence, Pinson had done a Ph.D. thesis at Rochester on water balance in man and knew already both the techniques and the problems.

This work showed in man the very rapid exchange reactions that the Hanford people were in the process of establishing in animals. Also, Pinson and Langham (1957) established that tritium (as HTO) passed inward through the skin at a rate comparable to that of insensible perspiration moving outward, a finding of immediate importance to maximum allowable exposures. The substance of this important paper can be gleaned from its abstract, reprinted below:

Using tritium water as a tracer in man, water absorption through the gastrointestinal tract began in 2-9 min and was complete in 40-45 min. The volume of water transferred from the intestine to the blood was linear with time and proportional to the volume of water ingested, within the range of 100-1000 ml. When exposed to HTO vapor via inhalation, man absorbed through the respiratory system 98-99% of the activity inspired. The activity in venous blood increased sharply during and shortly after inhalation exposure, after which it declined exponentially to equilibrium with a half-time of about 12 min. The average dilution volume in five experiments on three normal males was 62.2% and the biological half-time of tritium in body water of eight males on ad libitum water intake averaged 11.5 days. At equal vapor pressures man absorbed HTO inward through the skin at a rate comparable to the rate of insensible perspiration. HTO appeared to diffuse across the inert barrier of the outer skin with a half-time of about 3 min. When man was exposed to an atmosphere containing HTO, the HTO entering the body through the total skin area was approximately equal to that entering through the lungs. Both man and rat slowly oxidized inspired HT to HTO. The radiation hazard from exchange of tritium with hydrogen of the tissues after chronic or acute exposure to HTO was small compared to the hazard from the amount of HTO necessary to induce the activity into tissue components. On the basis of human data, the maximum permissible body burden of tritium was calculated to be 3.7 mCi, and the maximum permissible concentrations of tritium oxide in air and water for continuous 24-hr exposure was estimated at 5×10^{-6} μ Ci and 0.1 μ Ci/ml, respectively. Adoption of the 1956 recommendations of the International Commission of Radiological Protection will result in the division of the above values by three.
(Pinson and Langham 1957, reprinted in 1980)^(a)

(a) This paper was selected as a "landmark paper" to be reprinted in the silver anniversary issue of *Health Physics*.

Other papers from Los Alamos bearing on this same subject concerned the specific activity of tritium in the organic components of skin (Pinson, Anderson, and Lotz 1952) and the biological effects of inhalation of high concentrations of tritium gas (Trujillo, Anderson, and Langham 1955). Collaboration of other staff, such as C. R. Richmond, came slightly later. Special note should be made of the fact that, although the publication dates are in the mid-1950s, the work on man was done quite early in the postwar era.

An experiment of special interest, indeed almost unique, is one on the RBE^(a) of the beta particles from tritium relative to ^{60}Co gamma rays (Furchner 1957). There have been hundreds of RBE determinations comparing one external radiation source with another.^(b) But when one of the radiations comes from an incorporated radioisotope, the situation becomes very complex because the metabolism (i.e., pharmacokinetics of the radioisotope) may result in dose rates that change rapidly with time if the isotope has a short half-life, is eliminated rapidly, or both. Furchner arranged the external radiation source (^{60}Co) inside a lead shield machined to produce an exponentially decreasing dose comparable to the declining dose from tritium as HTO by slow movement of the source within the shield. This ingenious device is shown in figure 8.15.

Using thirty-day mortality in CF1 mice as the criterion and the intercept constants from probit mortality curves, Furchner calculated an RBE of 1.72 ± 0.13 . It happens that this value agrees with others obtained without the special effort to match dose kinetics and with varying criteria (e.g., Thompson 1954; Storer et al. 1957; and Los Alamos Scientific Laboratory reports in 1953 and 1954). But the RBE values are so small anyway that this may not have been the best test system for analysis of the point at issue. Nevertheless, the point is important. While Sacher (1954) appears to have had some interest in what he terms the lethality function for exponentially decaying exposures, there does not seem to have been as much general application of this

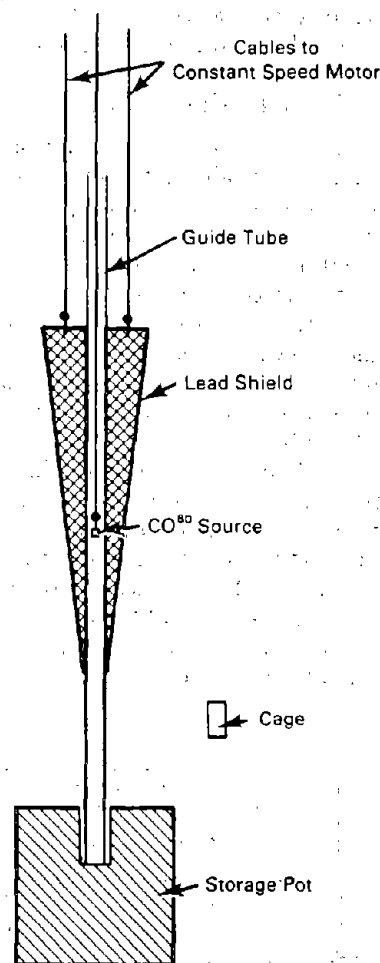


FIGURE 8.15. Lead shield for exponential exposure of CF1 mice to Co^{60} γ -radiation. (Redrawn from Furchner 1957. Reprinted with permission of Academic Press, Inc., Orlando, Florida, copyright 1957.)

(a) See discussion of this terminology on page 387.

(b) Los Alamos was a center for such work. Witness an over-one-hundred page paper by the Los Alamos staff in 1957 (Storer et al. 1957).

idea as might be expected. Obviously, when half-lives and/or retention are quite long, there is little hope of obtaining a conventional RBE between an internal emitter and an external source, unless the external exposure is very long term. Nevertheless, it is surprising that more work has not been done in this area after Los Alamos showed the way. It might have particular pertinence in cases where a component of chemical toxicity from the radioelement is suspected. Elimination of any dose-rate factors would be essential in such cases.

4. Fission Products and Other Radioisotopes

It was natural that, despite the plethora of work around the country on fission products and fallout, the Los Alamos Health Group should get deeply involved. Much of this work is more pertinent to chapter 13, where it will be reviewed. But some is of quite general significance and should be reviewed now.

Central to this is work organized by Chester W. ("Chet") Richmond during his years at Los Alamos. With his colleagues Furchner, Drake, London, Thomas, and others, a systematic study was made of the comparative metabolism of radionuclides in mammals. In contrast to the king-sized long-term experiments going on elsewhere, the Los Alamos work built upon a series of discrete experiments. There were several animal species and several routes of administration in each study.

Part of the importance of this work was the methodology. The Los Alamos people built one of the early whole-body counters using photomultiplier tubes and a large volume of liquid scintillation fluid (see chapter 17). They also built scaled-down versions suitable for doing whole-body counts on small animals. In the early work, this was called simply "Small Animal Counter." Later, this type of device was called "LASAC I," while the larger device in which large animals and humans were measured was called "HUMCO I." A diagram of the small animal device is shown in figure 8.16.

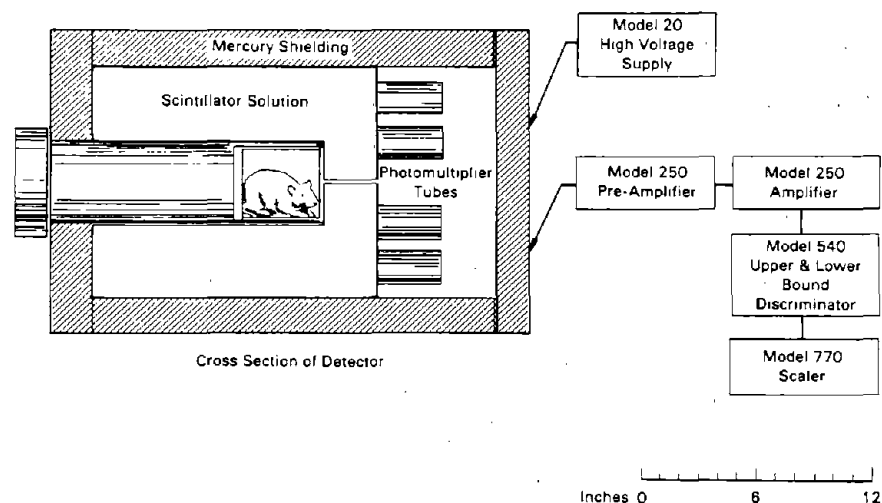


FIGURE 8.16. Small animal counter, Los Alamos Scientific Laboratory. (Redrawn from Woodward, Richmond, and Langham 1956.)

The system provided extremely sensitive 4π -steradian geometry. Thus, very small amounts, truly tracer amounts, of the radionuclides could be employed, and adequate data could be obtained over reasonably long periods. Also, a few of the elements were administered, in very low doses, to man so that extrapolation to man could be checked by real data points on man.^(a)

Equations for retention in the whole body as a function of time were derived by computer techniques. In nearly every case, the data could be fitted by one to three exponential terms, seldom by a power function. (Remember the Chicago work discussed earlier applied a power function to some of the bone-seeking elements.) Special attention was given to the longest-term component because of its pertinence to the occupational exposure guides. By taking the integral of the individual effective^(b) retention functions from time zero to time infinity, an entity called the metabolic equilibrium factor could be derived. This expressed the relation of the final equilibrium body content for that particular species and the particular route of administration to the unit dose, i.e., daily intake, assuming intake was quasi-continuous as postulated for deriving the exposure limits. In nearly every case, this factor increased with body weight. A general relation of the form:

$$E. F. = a (\text{body weight})^k$$

where E. F. is the Estimated Equilibrium Factor expressed as a multiple of the daily dose; and the constants a and k are derived from least-squares fits of the data to regression lines.

In most cases, this relation was linear. It was complex for ^{60}Co , i.e., the whole-body retention appeared to be longer in mouse than in the rat, monkey, or dog. This latter was attributed to species differences in the behavior of vitamin B_{12} , of which cobalt is a part. In general, this relation to body weight supported extrapolation to humans and estimation of MPC^(c) values from the extrapolated animal data.

The first report in this systematic study was in a paper given at the first meeting of the Health Physics Society (Woodward, Richmond, and Langham 1956). It concerned ^{24}Na , ^{42}K , ^{86}Rb , and ^{134}Cs given orally or intravenously. The subjects were rats, mice, and a single human volunteer for the cesium experiment. The elements used obviously ranged from some of primary interest to the physiology of electrolytes, through some of interest because they are fission products or activation products, to some included because of their general importance in toxicology.

The bulk of the work was set out in eleven papers entitled, "Comparative Metabolism of Radionuclides in Mammals," all published in *Health Physics*. An overview of the series is given at the top of page 458.

How the body-weight-equilibrium-factor relationship worked out for four elements is given in figure 8.17A, B, C, D.

(a) As Richmond stated (1979), they felt that unwillingness to accept personally administration of isotopes at levels well below the allowable limits would imply lack of confidence in those limits. Some of this was before the As Low As Reasonably Achievable (ALARA) principle had been adopted.

(b) Effective, meaning that both physical decay and biological elimination were included.

(c) Maximum Permissible Concentration, the parameter used until very recently for expressing allowable intakes of radioelements.

Paper No.	Element	Animals	Routes of Administration(a)	Reference
I.	Zinc-65	Mouse, rat, dog, human	oral, i.v.	Richmond et al. 1962
II.	Iodine-131	Mouse, rat, dog, monkey	oral, i.p.	Furchner and Richmond 1963
III.	Manganese-54	Mouse, rat, dog, monkey	oral, i.v., i.p.	Furchner, Richmond, and Drake 1966
IV.	Silver-110m	Mouse, rat, dog, monkey	oral, i.v., i.p.	Furchner, Richmond, and Drake 1968
V.	Iridium-192	Mouse, rat, dog, monkey	oral, i.v., i.p.	Furchner, Richmond, and Drake 1971a
VI.	Niobium-95	Mouse, rat, dog, monkey	oral, i.v., i.p.	Furchner and Drake 1971
VII.	Ruthenium-106	Mouse, rat, dog, monkey	oral, i.v., i.p.	Furchner, Richmond, and Drake 1971b
VIII.	Beryllium-7	Mouse, rat, dog, monkey	oral, i.v., i.p.	Furchner, Richmond, and London 1973
IX.	Selenium-75	Mouse, rat, dog, monkey	oral, i.v., i.p.	Furchner, London, and Wilson 1975
X.	Cobalt-60	Mouse, rat, dog, monkey	oral, i.v., i.g.	Thomas et al. 1976
XI.	Tin-113	Mouse, rat, dog, monkey	i.v., i.g., i.p.	Furchner and Drake 1976

(a) i.v. = intravenous, i.p. = intraperitoneal, i.g. = intragastric. Not all routes were used for all species.

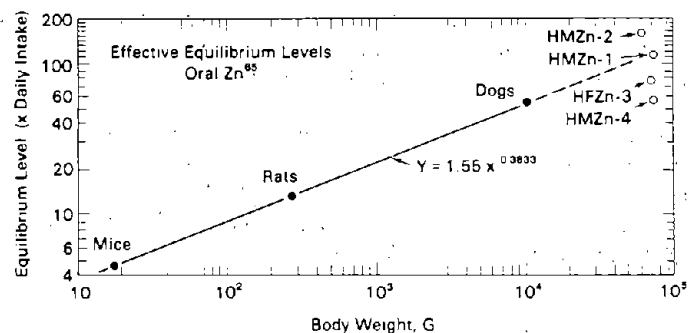


FIGURE 8.17A. Interspecies correlation between Zn^{65} equilibrium level and body weight. Regression line is based on mice, rats, and dogs. Open circles represent experimentally determined values for human subjects. HM = human male; HF = human female. (Redrawn from Richmond et al. 1962. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1962.)

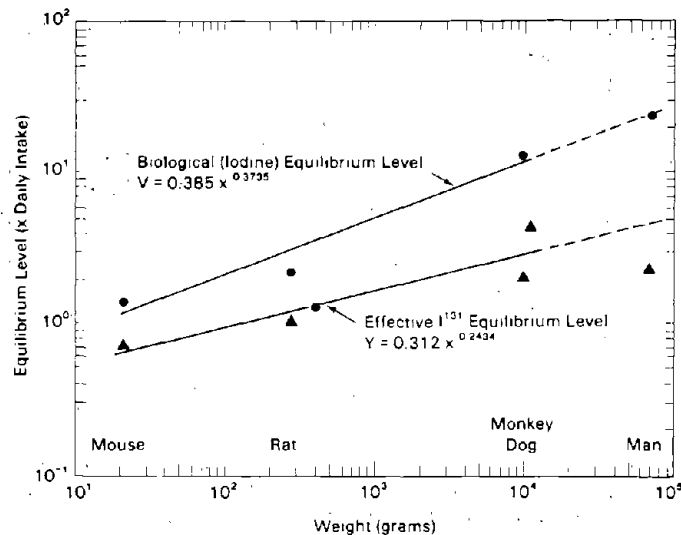


FIGURE 8.17B. Interspecific relation of body weights and equilibrium levels for ^{131}I . The equations are least-squares fits to the open data points. The solid points are from LAMS-2526, p. 364, 1961. (Redrawn from Furchner and Richmond 1963. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1963.)

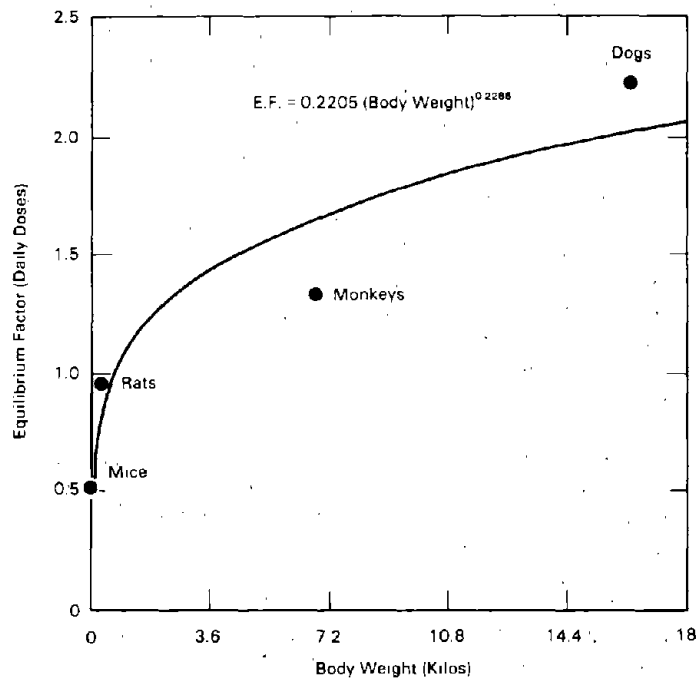


FIGURE 8.17C. Relation between equilibrium factor and body weight for ^{54}Mn . The smooth curve is the least-squares fit to these points: $\text{E.F.} = 0.2205 (\text{body weight})^{0.2286}$. (Redrawn from Furchner, Richmond, and Drake 1966. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1966.)

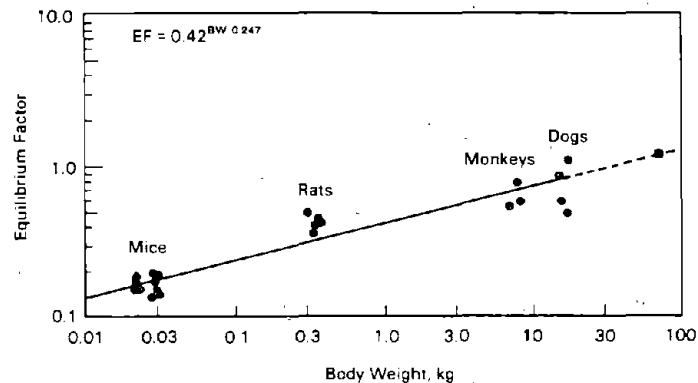


FIGURE 8.17D. Interspecies correlation between ^{70}Be equilibrium levels (estimated from single oral doses to mice, rats, monkeys, and dogs) and body weights. The broken portion of the curve is an extrapolation to a 70-kg body weight. (Redrawn from Furchner, Richmond and Drake 1968. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1968.)

The cases where the equilibrium amount is close to or even less than the daily dose represent either very poorly absorbed or very short half-life elements, while high equilibrium levels result when the converse is true. The equilibrium factor (E.F.) will, of course, be a function also of the route of administration and may be very different after intravenous administration of an element that is poorly absorbed from the gut since the E.F. is expressed as a product of the daily dose. This can be seen in the tables of several of the papers.

Special note should be made of the following findings:

1. The whole-body retention of iodine is about equally divided between thyroid and pelt. It is customary to think of the burden as wholly in the thyroid because of its high concentration there.
2. The differential of the retention curves can be used to express excretion rate.
3. Parabolic relations between species weight and daily turnover are quite general for mineral metabolism both in this study and in the literature. Similar relations hold for other physiological processes.
4. The same element can require different numbers of exponential terms to express retention after different routes of entry.
5. Cobalt is the maverick in this particular series. The data for the rat fit a logarithmic plot, i.e., a power function (Richmond and London 1968) and so can the data from the mouse. But the monkey and dog do not show any decrease in rate with time.
6. Many of the calculated MPC values agree well with the then-current ICRP-NCRP numbers. Others are at variance by factors from two to five or more. The same goes for parameters like gastrointestinal-tract absorption. But only in the case of cobalt would extrapolation from rodent data to man be seriously misleading (more in chapter 16).

Richmond (1979) states that these isotope metabolism figures from Los Alamos were given special credence by those (e.g., Walter Snyder et al.) seeking biological input data for the MPC calculations of ICRP and NCRP. This was because

the very low levels ensured no component of chemical toxicity or radiation damage in the results.

There were other papers correlated closely with this series but not numbered in it. These, plus some abstracts for meetings (e.g., Richmond, London, and Furchner 1964), sum to a very useful and sophisticated set of contributions to our understanding of the metabolism of many elements.

More of the Los Alamos work on fission products will be reviewed in consideration of the research specifically oriented toward the problems of fallout (chapter 13).

5. Comment

These few pages, devoted as they are to postwar work only on the actinides, tritium, and to fission products, can give only a cursory idea of what developed in the Health Sciences at Los Alamos between 1949 and the 1970s, particularly since two major areas of direct pertinence to internal emitter research have been postponed for the most part to later chapters. The "hot particle" problem occupied much of their attention but is more appropriately reviewed in connection with inhalation toxicology. Much of their participation in nuclear testing, environmental contamination, development of a nuclear-propelled rocket, radioisotope heat sources, etc., is deferred for later discussion. And, finally, it takes only a cursory glance at a typical annual report to see that the laboratory engaged in a large amount of work with external sources and full-fledged programs in molecular and cellular radiobiology. Yet, the names we immediately associate with Los Alamos in the postwar years are of those who had most to do with the internal emitter research: Wright Langham, E. C. Andersen, Jack Furchner, Chet Richmond, Jack Healy, Harry Schulte, Tom Shipman, Robert Thomas, and George Voelz, in situ, and Louis Hempelmann acting partly in situ and partly from Rochester.

V. Other U.S. Work

Postwar biomedical work on the fission products and actinides in the United States has now been reasonably thoroughly reviewed in this chapter, except for those topics put over for later discussion. Some laboratories that were active in the field during the war years (e.g., Rochester) concentrated on other areas and/or basic work not generated by the specific problems of any particular element. Others entered the field for a relatively circumscribed, yet significant, enterprise. This section will review very briefly some of these activities. They are not all laboratory research; but all are pertinent.

A. Colorado State University

The Department of Radiobiology and Radiology at Colorado State University (CSU) has been operating a large barrier-maintained beagle colony primarily for studies of external radiation effects as a function of age. This was supported initially by the U.S. Public Health Service and by later-spawned agencies. They also have had interests in the uranium miner problem, in environmental pollution, and have had a strong graduate teaching program.

Apparently because of their close proximity to the Rocky Flats plutonium plant, they undertook work directly related to entry of plutonium into the body via wounds. Some of the work was collaborative with the Rocky Flats staff. They

implanted samples of "high-fired" PuO_2 (calcined at 850°C) and of plutonium nitrate in the left foot pad of the dog. They then measured translocations, effects of chelating agents, and the relative behavior of ^{241}Am from the decay of ^{241}Pu . Indeed, they used the x ray from this isotope to help measure the translocation.

One of the early papers from this group was a report of lymphoma developing in the regional lymph nodes of a dog receiving air-oxidized plutonium by subcutaneous injection (Lebel et al. 1970). Most of the rest of the work concerned metabolism of the plutonium from implanted sources.

In a paper given at the Hanford symposium on transuranium elements in 1971, Watters and Lebel (1972) summarized the metabolism work. The abstract is given below:

Air oxidized plutonium, $\text{Pu}(\text{NO}_3)_4$ and high fired PuO_2 (850°C) which had known amounts of ^{241}Am were implanted over the left metacarpus in beagle dogs and the concentrations of ^{239}Pu and ^{241}Am in various tissues were measured as a function of time. The effect of DTPA therapy upon organ depositions was also studied.

For air oxidized plutonium, rapid movement of ^{239}Pu and ^{241}Am to the proximal lymph node (superficial cervical) has been observed by in vivo counting. Approximately 3% of the implant material reached the lymph node within 2 weeks and continued an exponential build-up to 17% at 1 yr.

Results of plutonium assays in blood indicate a 14-fold increase in movement to the circulation from the $\text{Pu}(\text{NO}_3)_4$ implants as compared with the air oxidized plutonium. This is supported by comparison of the depositions in the liver and the proximal end of the femur where the $\text{Pu}(\text{NO}_3)_4$ experiment produced twenty-four times higher levels of plutonium than did the air oxidized plutonium experiment.

The effect of DTPA therapy was greater for the nitrate than for the air oxidized plutonium implants. (Watters and Lebel 1972)

Bistline, Watters, and Lebel (1972) compared the translocation dynamics in the same system of americium and plutonium in two forms. They comment especially on the accumulation in the proximal lymph node(s) and differences between this and experiments done two years earlier by Johnson and Watters (1970). (a) In the 1972 experiments, the lymph nodes reached a peak concentration at about fifty days, then fell off again, while in the earlier work build-up continued throughout the one-year study. The particle sizes of the implanted material were considerably larger in the earlier experiment, and this is taken as an explanation for the difference.

Of considerable significance to any prognosis of systemic build-up from wounds was the finding that the speed of initial translocation depends more upon the position of the implant than on the amount of plutonium present.

A third paper at the same symposium (Gomez, Lebel, and Watters 1972) looks at the effect on the translocation of excision of a cervical lymph node on the side of the implant. Even though it was clear that other lymphatic nodal tissue remained, the result was an increase in plutonium levels in liver, spleen, and hepatic lymph nodes. The authors comment on the advisability of removal of lymph nodes in cases of human contamination by wounds. The rationale for this seems somewhat shaky since it might not necessarily be better to have more plutonium in liver and spleen in lieu of an amount in a peripheral lymph node.

With this problem partly in mind, Gomez, Lebel, and Watters (1972) tried delaying the removal of the lymph nodes until fourteen days. In this way, they

(a) Rapid movement to lymph nodes was first shown in this report.

expected to be able to remove significant amounts of plutonium and perhaps not stimulate translocation of the remainder. There was indeed a "large amount" of plutonium in the excised lymph nodes, but transfer to liver, spleen, and hepatic lymph nodes increased significantly nevertheless.

Although the CSU group has continued active in many aspects of environmental contamination with plutonium, the type of work involved above does not seem to have gone much further there.

B. New York University Institute of Environmental Sciences

This organization has had a significant impact on internal emitter toxicology. Nearly all of the work pertains to either inhalation toxicology, environmental pollution, or elements such as radon and its daughters, polonium, uranium, thorium, etc., which we have already reviewed. The exception is some work with americium and curium in man and the baboon. For many reasons, it is more convenient to take up these transplutonic elements as a group in the final section of this chapter.

C. Oak Ridge Institute of Nuclear Studies and University of Tennessee

For many years, two aspects of the postwar work on fission products and actinides were pursued in depth under the general aegis of the rather loosely organized Oak Ridge Institute of Nuclear Studies (ORINS) (see Appendix B).

1. The University of Tennessee-Atomic Energy Commission Farm (UT-AEC Farm)

This "farm" and associated laboratory were developed initially as a holding operation for cattle and other large animals exposed to fallout from weapons tests. An extensive experimental program was developed under the direction of Dr. Cyril Comar until he moved to Cornell. In later years, Dr. T. R. Noonan managed the research program. For some years, its output and financing were funneled through the Oak Ridge Institute.^(a) All of the work bore on fission products in animals, plants, and the environment. For convenience, it will all be regarded as work stimulated by the problems of fallout and be discussed in chapter 13. But it contributed much to understanding the basic behavior of these elements in large and small animals as well as in plants and ecosystems. For this reason, it needs to be recognized here even though specifics are deferred.

Also to be recognized here but discussed in connection with contributions to basic science is the work on radiocolloids done by G. K. Schweitzer at the University of Tennessee (e.g., Schweitzer and Jackson 1952).

2. Medical Division of Oak Ridge Institute of Nuclear Studies

We reviewed in section II B the systematic study of the lanthanides at Berkeley. We also cited the general compendium on rare earths gathered together by Granvil Kyker of the Medical Division of ORINS. Probably no other single laboratory has looked as hard at or made as many trials for possible applications

(a) In more recent years, it has become the Comparative Animal Research Laboratory (CARL). Other key staff members are mentioned in chapter 13.

in nuclear medicine of radionuclides in the lanthanide-rare earth series. In the process, they engaged in much background work on the behavior of these elements, both in vitro and in vivo in animals (Kyker) and man (Andrews). There was collaboration with the Spedding group at Iowa State University in obtaining and characterizing the compounds required. Since the primary thrust of this work is in the field of nuclear medicine, the background as well as the clinical work will be reviewed briefly in the chapter on that subject (chapter 20).

D. University of Rochester

It should be apparent from other chapters (1, 2, 3, 4, 9, 10, 14, 19) that the postwar work at Rochester with uranium, radium, radon and its daughters, polonium, and many miscellaneous nuclides whose toxicity needed study had deep significance for all of the problems of internal emitter toxicology. But the wartime work with plutonium did not continue except for inhalation studies.

The only major experiment at Rochester within the purview of this chapter was work sparked by Lawrence W. Tuttle on ^{90}Sr in monkeys with spill-over work in rats. The animals imbibed the isotope in the drinking water in the case of rats, by gavage in the monkeys. Hence, the experiment was comparable to, although smaller than, those with swine at Hanford and with dogs at Davis. The primary novel feature was use of a primate as well as the rat. In this it paralleled the effects phases of the work at Berkeley on primates.

The methodology was given in a University of Rochester report (Tuttle et al. 1959), pathology in rats by Casarett et al. (1958), and the late pathology in both rats and monkeys by Casarett, Tuttle, and Baxter (1962). This last report is full of detail on the rodent, which can be reviewed better along with other effects experiments in chapter 13. Let it be said here, however, that there were only seven monkeys in the experiment. These were at two dosage levels, 500 μCi (three monkeys) and 1,000 μCi (four monkeys). Body burden at death ranged from 33 to over 200 μCi . The cause of death was given as parasites in two animals, one at each dosage level, as pancytopenia in one of the higher-dose animals with a calculated skeletal dose of 4,500 rad, and as leukemia in one of the lower-dose animals with a calculated skeletal dose of 4,300 rad. Only two, both in the higher-dosage group, died with tumors of the type usually attributed to ^{90}Sr deposition in bone. One was a chondrosarcoma in an animal with 9,500 rad calculated skeletal dose. The other was an osteosarcoma in a monkey with a calculated dose of 4,700 rad.

It appears that most of the pathologic effects in this work were gleaned from the Long-Evans rats.

Another piece of work of pertinence is a study of the renal excretion of strontium and calcium in dogs by Della Rosa, Smith, and Stannard (1961). This work indicates that there is discrimination toward calcium retention and away from strontium retention by the dog kidney. (More in chapter 13.)

Of special interest to the theoretically inclined is the analysis by Blair (1968) of radiation dose-time relations for induction of bone and skin tumors. From a kinetic analysis of already published data, he postulates that there are two mutually exclusive routes of tumor induction in both rat skin and dog bone. The skin received brief doses of beta radiation, while the bone doses were from injections of ^{239}Pu , ^{226}Ra , ^{228}Ra , or ^{228}Th , all alpha emitters. The radioisotope data were primarily from the Utah experiments, the beta exposures of skin in rats from work of Albert and colleagues at New York University. As Stannard lamented

earlier (1973), these ideas could now be tested with longer-term, more secure data, but Harry Blair is not here to do it, and others have not picked up the thread.

Incidentally, a toxicity ratio could be calculated from the values of "K," the so-called initiating dose for the various elements. It comes out quite close to the ratios we have already become familiar with: using ^{226}Ra as the standard, the ratio for ^{239}Pu is 7, for ^{228}Ra is 1.7, and for ^{228}Th is 4. The analysis also provided a factor for time to develop a tumor. But this was not so amenable to analysis. General summaries were written by Stannard (1973, 1975b).

E. Other Laboratories and Organizations

Despite the length of this chapter, the biomedical work done at U.S. laboratories since World War II on actinides and fission products is far from being completely cited. Since the reader may wish to know what went on at a few laboratories not included above, some additional remarks are needed.

1. Cornell University

Cornell University developed, at about the middle of the period covered by this chapter, a laboratory of Physical Biology as part of its Veterinary College. Dr. Cyril Comar moved up from Oak Ridge and assembled a staff with interests in mineral metabolism. The *modus operandi*, at the outset at least, was a continuation of the broad studies on fission product movement in animals and plants, and to a lesser extent effects started at the UT-AEC Farm in Oak Ridge. Interspersed was a gradually increasing amount of work bearing on mineral metabolism *per se*. It is to our advantage to view the details of the Cornell work in chapter 13 along with other work stimulated by the problems of fallout.

2. Oak Ridge National Laboratory

a. Biology Division

The Biology Division of Oak Ridge National Laboratory stayed clear of radioisotope toxicology, as defined for this book, until almost the end of the period of this chapter. In the midseventies, a collaborative effort between Argonne National Laboratory and the Oak Ridge Biology Division in the field of genetics began. All through the years of the Russells' "megamouse" experiment using external radiation, there had been concern about possible genetic effects of internally deposited radionuclides. But data were limited to single-cell or colony systems, to measurements of chromosomal aberrations, and to assay of gonadal content (e.g., Richmond and Thomas 1975; Brooks, personal communication) of important elements for calculation of dose. The effects studies were summarized, for example, in reports from Argonne (Grahm et al. 1979), from Lovelace (Brooks 1975), and in work done abroad.

Recently the Russells' powerful specific locus mutation technique was applied to mice injected with ^{239}Pu citrate. The dose was $10\ \mu\text{Ci/kg}$ body weight or about $0.25\ \mu\text{Ci}$ per mouse. The plutonium was in monomeric form. The solutions were prepared and injections performed by Argonne personnel (Arthur Lindenbaum and later Douglas Grahm).

Only one publication has appeared to date concerning the results of this work, an abstract by Russell et al. (1978). This showed that a highly significant

increase in mutation frequency was produced by this dose of plutonium. The workers are in process of gathering sufficient data to provide an adequate estimate of the genetic hazard of plutonium.^(a)

b. Health Physics Division

The Health Physics Division at Oak Ridge National Laboratory has been the mecca for the problems of internal dosimetry and the derivation of intake limits for radioisotopes; as we shall see in chapter 16. They have also made occasional forays into experimental work, as we saw in the chapter on uranium, and will see when we discuss work such as that by Isabel Tipton aimed directly at the determination of parameters to be entered into the dosage calculations.

3. Health and Safety Laboratory, New York (Environmental Measurements Laboratory)

The USAEC Health and Safety Laboratory (HASL) in New York City (now the Environmental Measurements Laboratory) has made significant contributions to research on fission products and actinides. Researchers there took special cognizance of methodologies; they have been extremely active in measuring and evaluating environmental contamination, both from fallout and from civilian nuclear operations; and they have provided important support for a large number of monitoring and radiation safety evaluations of specific sites. It is appropriate to reserve the details for the chapters on fallout and the environment and the practical problems to be reviewed in chapter 16. In general, their contributions were accessory to internal emitter toxicology as we are reviewing it, but they have made much of the research better and more responsible to problems in the field. Also, individuals from the HASL staff have been deeply involved with many research projects domiciled in other places.

4. University of California, Los Angeles

An AEC project was developed at the University of California, Los Angeles (UCLA) after the war years, patterned much after the Rochester Project that Stafford L. Warren had helped to initiate in the MED days. The UCLA project has been deeply involved in biomedical aspects of the weapons testing program, especially environmental contamination, in nuclear medicine, and in basic radiobiology. It also has had an active educational program. The work associated with the weapons tests and fallout, and the later environmental work will be reviewed in chapters 13, 14, and 15; the work in nuclear medicine in chapter 20. The rest is outside our purview.

5. U.S. Atomic Energy Commission, Division of Biology and Medicine; U.S. Energy Research and Development Administration, Division of Biological and Environmental Research; U.S. Department of Energy, Office of Health and Environmental Research

That the role of the "Headquarters" scientific staff was much more than administrative should be obvious from the numerous references already made to their

(a) Unpublished observations supplied to the author as part of his functions with the National Council on Radiation Protection by A. L. Brooks, the Chairman of a special Task Group on Genetic Risk from Internal Emitters, indicate that, for the present, the hazard can be considered comparable to an equivalent dosage from external radiation.

work in specific areas. Many more such references will be made as we proceed. But the field of fission products and the actinides came in for especially intensive attention from within the Headquarters operation.

When Ernest Sternglass began his series of allegations on excess infant mortality resulting from the release of fission products from weapons tests and later from power reactors, the Headquarters staff had to do much more than get and coordinate opinions. They became the vortex for much of the polemic. We shall review this saga in chapter 12.

In the actinide field, the Headquarters staff was responsible for several activities of wide scope and considerable depth to evaluate the status of our knowledge. Much of this was forced by the breeder reactor concept, the prospect of greatly increased amounts of plutonium and other actinides in the nuclear industry, and potentially in the environment, and the public reactions to these.

The first action occurred near the end of the existence of the AEC. It consisted of the development "in house" of a series of Plutonium Task Forces responsive to a Plutonium Committee. The central problem was the defensibility, or lack of it, of current MPCs for plutonium and other transuranic elements. But the documents ranged over all of the research in the area.

The second developed early in the ERDA period. It included a large workshop in 1977 at the Battelle Seattle Research Center to address the current research needs in actinide biology. This was organized by Dr. Patricia Durbin from UCRL-Berkeley. There were summary presentations by a considerable cross section of the research community who had been admonished by the Chairman to "Think Actinides." There followed an executive session in which the Headquarters staff used the information presented, as well as background material, to help shape recommendations for ongoing programs. The summary of actinide biological research, 1943-1977, prepared for this meeting by Durbin is especially useful for historical perspective. It is available as Appendix A to CONF-770491 (Durbin 1978b). Naturally, the details of the executive session have never been made available, since they involved decisions regarding specific programs and people. We might have heard more of the decisions if ERDA had not been reorganized, with staff changes, to become part of the Department of Energy (DOE) soon after these events.

A third effort of more than routine dimensions was an internal emitter advisory committee in the Division of Biomedical and Environmental Research of ERDA. This group, which was something of a moving target, stimulated summaries of the work supported by ERDA on metabolism, dosimetry, and effects of transuranium and transplutonium elements and specific recommendations for continued or new work on these as well as other radioisotopes. Frequently, the opinions of outside consultants were folded into the eventual documents or attached as supplements.

Details of the reports are presumed to be proprietary since they were strictly "in house" documents.^(a) Yet, some of the ideas found in them brought into focus neglected as well as overworked areas. In the present context, let it be

(a) The author had the privilege of rummaging through numerous files concerning these activities during one of several visits to the current Office of Health and Environmental Research in the Department of Energy. Thanks are due especially to Dr. William J. Burr and his secretarial staff for making the process relatively easy.

said that these activities at Headquarters frequently added essential information or essential perspective that kept support flowing for laboratory and field activities or arranging gradual termination.

Finally, the Headquarters staff wrote hundreds of pages of documents for the epidemic of hearings in the mid-1970s, sponsored especially, but not exclusively, by the EPA and the Nuclear Regulatory Commission (NRC), as well as by ERDA and DOE. Documents that summarize internal emitter research are cited from time to time in connection with specific areas.

6. Federal Radiation Council

The Federal Radiation Council (FRC) will be described in chapter 16 since it was concerned primarily with standard-setting. It, like the AEC and ERDA, stimulated many reviews and evaluations. Some were done earlier than the activities described in the previous section. They were accomplished largely by bringing in advisory groups or asking the National Academy of Sciences (NAS) to prepare evaluations.

One evaluation with the most pertinence to the subjects of this chapter is a report dated December 1964, by an NAS Advisory Committee to the FRC (NAS-FRC 1964). This was a full review of all aspects of the implications to man from internally deposited ^{89}Sr , ^{90}Sr , and ^{137}Cs . The report considers radioactive cesium like whole-body exposure and lists the chief concerns as genetic damage, leukemia, and other neoplasms, while the localized strontium exposure to bone and bone marrow is considered prone to produce leukemia and disturbances of growth and development of the skeleton and teeth, in addition to producing bone tumors. The section on genetics takes special pains to consider findings since the National Academy-National Research Council BEAR (Biological Effects of Atomic Radiation) reports in 1956 and 1960. In general, the estimate of genetic risk was regarded as being reduced by the new work. The report also summarizes genetic studies on strontium isotopes done abroad.

7. National Council on Radiation Protection and Measurements

The NCRP, a Congressional charter organization,^(a) is primarily organized around promulgating recommendations for allowable radiation exposures or intakes of radioactive materials. But increasingly it has also been publishing reports that are state-of-the-art summaries of their subject fields. They also issue timely summaries of measurement techniques.

Reports with direct bearing on postwar fission product or actinide research concern ^{85}Kr in the atmosphere (NCRP 1975); tritium measurement techniques (NCRP 1976); ^{137}Cs from the environment to man: metabolism and dose (NCRP 1977); physical, chemical, and biological properties of radiocerium relevant to radiation protection guides (NCRP 1978); and tritium and other radionuclide-labeled organic compounds incorporated in genetic material (NCRP 1979). Other reports were or will be cited with the relevant subject matter (e.g., chapter 3, chapter 16).

While these reports bring together much of the experimental work with a bearing on the development of standards, they also address most of the basic questions and problems remaining to be solved.

(a) More history of NCRP in chapter 16.

VI. Work Abroad

The charter for this book (see foreword) puts severe constraints on the amount of space that can be devoted to work in other countries. Even if it were not the intent to focus primarily on the work of the MED, the AEC, and successor organizations, the mass of material on fission products and the actinides worldwide would overwhelm us if we attempted any detailed review. Yet, there was not only a considerable volume of work abroad, it was, much of it, of such high quality that total omission could not be contemplated.

Soon after World War II, the United Kingdom, Canada, France, and the Soviet Union developed nuclear energy resources with great dispatch. Along with this came biomedical research. Some of it duplicated almost exactly work that had been done in the earlier American operation. This can be ascribed partly to the time required for declassification and publication of the U.S. war work. Also, it represents partly the desire of each laboratory to apply its own idiosyncratic approach or the special nature of its field problems.

Other countries, such as Austria, Belgium, Czechoslovakia, Denmark, India, Italy, Japan, the Netherlands, Norway, Poland, South Africa, Sweden, Switzerland, and West Germany either expanded on activities they already had going or built research programs as needed. The U.K., French, and Soviet work were the most extensive.

Particular interest attaches to the following from the United Kingdom:

1. Actinide and strontium work at the Medical Research Council's (MRC) Bone Research Laboratory at the Churchill Hospital, Headington, Oxford, where Dame Janet Vaughan, Betty Bleaney, and associates did wide-ranging studies with the bone seekers in rabbits. Results paralleled U.S. work in general. There were many opportunities to exchange ideas and results. The chief difference seems to be a larger role of soft-tissue changes in the rabbits and, because of this, changes in the thinking of this group.
2. Basic chemical and biochemical reactions of actinides with constituents of blood and bone by David M. Taylor and A. R. Chipperfield at the Institute for Cancer Research, Sutton, Surrey, wherein the transport of plutonium as a complex with ferritin was nailed down.
3. Questions of bone modeling and the target cells in bone by F. W. Spiers at the Department of Medical Physics, University of Leeds.
4. Much metabolism and mechanism work at the MRC Radiological Research Unit at the Atomic Energy Research Establishment at Harwell (J. Vennart, J. F. Loutit, R. H. Mole, et al.). This included deposition in gonads and cytogenetic studies.
5. A broadly based summary of plutonium toxicology from the MRC Headquarters.
6. Short, yet significant and timely commentaries on both broad and specific problems from the Radiological Protection Service and Board at Sutton, Surrey.

Much of the U.K. work is cited in books and chapters prepared by U.K. authors and referenced in this and other chapters in connection with specific topics. Special mention should be made here of the book on strontium metabolism edited by Lenihan, Loutit, and Martin (1967) and on low-level irradiation with emphasis on strontium by Loutit (1962), as well as the comprehensive

reviews of Vaughan (1973) on plutonium in the skeleton, by Taylor on the chemistry of plutonium (Taylor 1973a) and the chemistry of the transplutronics (Taylor 1973b).

The Soviet literature is extensive around both actinides and fission products. Much of it comes from the Institute of Biophysics, Ministry of Public Health in Moscow (Yu. I. Moskalev, L. A. Buldakov, E. R. Lyubchanskii, A. P. Nifatov, and colleagues).^(a) Much of the work with plutonium was translated by A. A. Horvath in Albuquerque, New Mexico, edited by R. G. Thomas at the Lovelace Foundation, and published in English under the title "Problems of Plutonium Toxicology" (Buldakov et al. 1970). Many other papers have been made available in the AEC Translation series from DOKLADY BIOPHYSICS.

It is of interest that the tendency for USSR work to dwell heavily upon neurological events, especially at the level of the synapse, seen extensively in their work concerning external radiation effects, is not so prominent in the research on internal emitters. The USSR work does tend to be more diversified, especially in later years, in contrast to what appears at times to be a single-minded obsession with bone tumors in contemporary U.S. work. It does not appear that the USSR work adds qualitatively new information in broad physiopathology to what came out of the MED work. But since the Russian work was done under less pressure than the MED work, it is sometimes more thorough and extensive, especially regarding general physiological effects.

The French laboratory at Fontenay-aux-Roses under the Commissariat à l'Energie Atomique includes much work on alpha emitters, as we saw in the chapter on radon and the uranium miners. J. Lafuma, H. Metivier, and J. C. Nénot are well-known names in internal emitter toxicology. Many other laboratories abroad had active radiobiology programs, but did not delve much into radioisotope toxicology.

VII. The Transplutonic Elements

A. Introductory Considerations

A small amount of work was done with the transplutronics at Berkeley during the war years (see for example, Scott, Axelrod, and Hamilton 1949), but most of the serious investigations were postwar. Americium-241 was added to the Utah beagle experiment in 1966 (^{249}Cf and ^{252}Cf , and ^{243}Cm and ^{244}Cm somewhat later), and there was additional work at Berkeley. On the whole, biomedical work with the transplutonic elements was rather scattered, both geographically and in the literature. Several laboratories were engaged with them, but none were involved in all-consuming efforts such as those we have seen for plutonium and the fission products.^(b) Until Pat Durbin put together her magnificent

(a) We have already noted the extensive work from the USSR with polonium and will see a little of their participation in the worldwide fallout programs in chapter 12.

(b) One reason was the relative scarcity of these substances for many years. Their production and accumulation in power reactors, and the need to handle them in fuel reprocessing and in waste disposal, generated considerable need to know, but availability in pure form for research does not automatically follow a need.

and comprehensive review, already cited (Durbin 1973), anyone trying to find out what had been done biomedically with the elements above plutonium in the periodic table was in for a tedious library search.

In chapter 7, section II, we reviewed the definition of the transplutonics and the wartime biomedical research done primarily at Berkeley. In section II of this chapter, we reviewed Durbin's systematic study of the lanthanides from lanthanum through lutetium, some comparisons of ^{241}Am to ^{45}Ca , of ^{241}Am to ^{239}Pu , and a summary of the review literature from Berkeley. In section III B, we saw the levels of ^{241}Am in the Utah beagle dog experiment (tables 8.5A,B), the retention equations for ^{241}Am and the two californium isotopes (table 8.7), and a few of the early results with californium.^(a) We also caught glimpses of transplutonic element research at Hanford and Los Alamos.

Our purpose here is to draw together a succinct summary of the conclusions of the research worldwide and its significance. First consider the fact that americium and curium (elements 95 and 96) maintain a very stable valence III state, whereas plutonium is stable in valence IV and VI states primarily. Consider also that the transplutonic elements are all radioactive, with shorter half-lives and thus higher specific activities than ^{239}Pu . Most are alpha emitters, although spontaneous fission occurs with some (e.g., ^{252}Cf). In either case, the biological effectiveness is high, especially relative to the lanthanides to which they are chemically analogous.

In a very useful summary table of mammalian studies in the review by Durbin (Durbin 1973, table 18.3), there are over fifty references to work with americium through 1972. Of these, approximately twenty-five were from U.S. laboratories (Berkeley, Hanford, Lovelace, N.Y.U., and Utah), eleven were from the Soviet Union (mostly the Institute of Biophysics in Moscow), eleven were from the United Kingdom (mostly the Institute for Cancer Research in Sutton, Surrey), two were from Lafuma's laboratory in France, and two were from the Nielsen group in Sweden. Of nine references to mammalian research with curium, six were from U.S. laboratories, two from France, and one from the USSR. There were two references to berkelium research, one each from the United States and the United Kingdom, and seven to californium, five from the United States and two from the United Kingdom. The distribution of work was about proportional to the number of references, except that the publications from the USSR were more summary in nature and gave less experimental detail. They alluded, however, to much more work to back up the conclusions given. The animals contributing were rodents, dogs, sheep, pigs, and monkeys.

The information discussed in the rest of this section was coordinated primarily from the Durbin chapter and from testimony on the biological effects of transuranium elements in experimental animals prepared by W. J. Bair for the 1974 EPA Hearings on Plutonium and Other Transuranium Elements (Bair 1974). Information in humans comes almost entirely from a few accidental exposures, particularly to americium, and uses in nuclear medicine (californium). We will take up these human exposures with others in chapter 16.

(a) Although the initial addition of transplutonics to the Utah experiment was a decade and a half ago, only a few dogs could be added at a time because of limitations of kennel space and care. Therefore, the story is only now becoming reasonably complete with more still to come.

B. Behavior in the Body (Metabolism)

The transplutonic actinides are in general more mobile in the body than is plutonium.

1. Absorption

Americium, curium, berkelium, californium, neptunium, and einsteinium are all more readily absorbed from the gastrointestinal tract than is even the most soluble form of ^{239}Pu , the nitrate. Corresponding salts of ^{238}Pu are more readily absorbed than those of ^{239}Pu . Some of the figures are given in table 8.10, taken from Bair (1974). It will be noted that some of the transplutonics are over an order of magnitude more readily absorbed from the intestinal tract than the same salt of ^{239}Pu .

TABLE 8.10. Gastrointestinal Tract Absorption of Transuranics in Rats (percent of administered dose)

Transuranic	Compound	Newborn	Adult
^{233}U	Nitrate	7	0.2
^{237}Np	Nitrate	1	0.9
^{238}Pu	Nitrate	2	0.03
^{239}Pu	Nitrate	0.3	0.003
	Chloride	—	0.007
	Oxide	—	0.0001
^{241}Am	Nitrate	9	0.07
	Chloride	—	0.03
	Oxide	0.5	0.01
^{244}Cm	Nitrate	6	0.2
	Chloride	—	0.05
	Oxide (aged in H_2O)	2	0.1
	Oxide (fresh)	0.3	0.03
^{249}Bk	Chloride	—	0.01
^{252}Cf	Nitrate	4	0.1
^{253}Es	Nitrate	4	0.03
	Chloride	—	0.06

Information in this table was developed from published reports and from results of current research at PNL by M. F. Sullivan.

Source: Reser from Bair 1974.

Durbin (1973) gives "best available estimates" of intestinal absorption (expressed as fractions of the dose) of multicharged cations in this series as:

^{144}Ce (valence III), 0.1% to 0.15%
 Trivalent actinides, 0.01% to 0.06%
 Pu (valence IV), 0.003% to 0.012%

She also gives absorption of actinide III chlorides as about five times as great as $^{239}\text{Pu}(\text{NO}_3)_4$ and from one-tenth to one-half as much as the intestinal absorption of $^{144}\text{CeCl}_3$.

Intramuscular absorption was again considerably ahead of ^{239}Pu (as either chloride or citrate).^(a) They do not show the long half-time component on the order of years seen in the absorption of plutonium from wounds.

Absorption through the intact skin has not been looked at extensively but seems to be of little importance unless the radioelement is in an organic liquid.

After inhalation, the transplutonics also showed behavior that contrasted somewhat with plutonium. There was less tendency for them to aggregate in lung, a phenomenon that we will discuss in chapter 9, and, in general, there was more rapid clearance from the lung to gastrointestinal tract or tissues. The aggregation in pulmonary lymph nodes is less marked than with plutonium.

2. Tissue Distribution

In general, all transuranics (i.e., neptunium, plutonium, and the transplutonics) exhibit similar tissue distributions in the long run. They all eventually settle in bone, as the organ of highest concentration, except for retention of very insoluble compounds in the lung. But in the early phases of absorption, the transplutonics, in general, go to soft tissue in larger quantity than does plutonium. This is especially true of liver, except for einsteinium. However, excretion from liver is fairly rapid too. This accounts in part for the emergence of bone as the organ of highest concentration eventually. Differences caused by chemical form, route of administration, or interspecies variations, may wipe out differences attributable to the element's properties per se, but the generalization holds when these other influences are factored out.

Kidney is frequently an important early deposition site. But urinary excretion may range from an important route of elimination to one of negligible importance for some compounds that are lost almost entirely via biliary excretion from liver to gastrointestinal tract. Cohen and Wrenn (1973), for example, concluded that all of the ^{241}Am deposited in the liver of baboons is excreted via the bile and feces.

Durbin (1973, figure 18.27) has prepared a model containing several compartments to express the metabolism of trivalent actinide elements in mammals. The model contains as major compartments plasma, liver, kidney, bone, incisors (in the rat only), and other soft tissues, with two-way interchange occurring between plasma and liver, bone, and other soft tissues, but only one-way transfer, outward, to kidney and incisors.

An example showing the time course of retention of ^{241}Am in liver, soft tissue, and skeleton is given here in figure 8.18 using Durbin's data from the cynomolgus monkey.

Note first that the points extend over a sufficiently long period to be significant to calculations of internal dose. Note also that the skeletal dose would be high primarily by tenacity of retention. The distribution among compartments is very dependent on the compound involved. Witness, for example, the difference between $^{241}\text{AmCl}_3$ and $^{241}\text{Am}(\text{NO}_3)_3$ illustrated in figure 8.19, taken from some of the Russian work. (Gonadal concentrations of the transplutonic elements appear to be about the same as those of plutonium.)

Cross-placental transfer is small for all the transuranics. However, americium and curium appear to cross the placenta less readily than does plutonium, a curious exception to their generally greater mobility.

(a) Durbin states that citrate complexes of the transplutonium elements are unstable in the body, and their behavior is thus identical to simple salts.

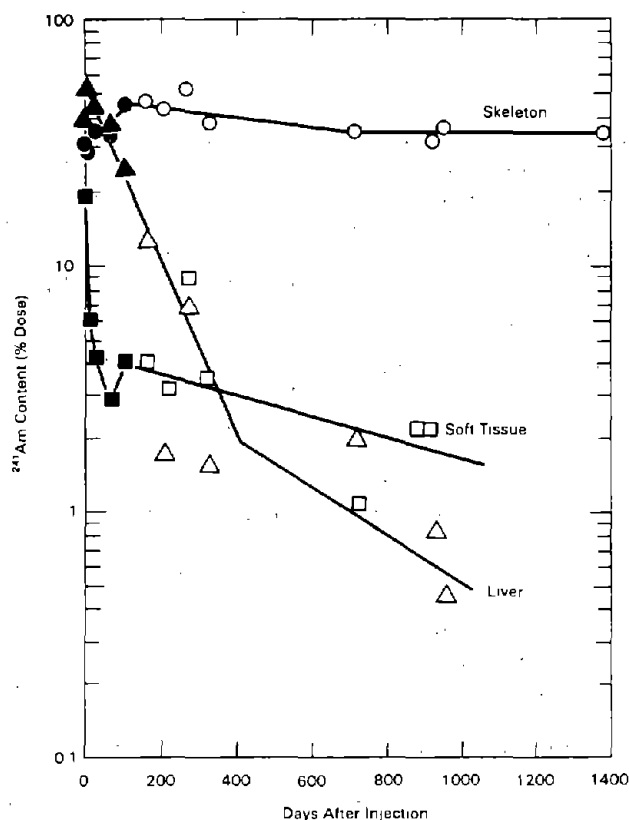


FIGURE 8.18. Retention of ^{241}Am in the skeleton, liver, and residual soft tissues of adult cynomolgus monkeys after intravenous or intramuscular injection of 0.44 to 0.87 $\mu\text{Ci/kg}$ of ^{241}Am citrate. Solid symbols represent pairs of monkeys and open symbols single animals. Data of Durbin, Williams, and Jeung 1972. (Redrawn from Durbin 1973, figure 18.21. Reprinted with permission of Springer-Verlag, Heidelberg, copyright 1973.)

At the microscopic level, the transplutonium elements show both similarities to and differences from plutonium. The ultimate site of deposition in bone appears to be similar for plutonium and, for example, americium: the mineralized bone surface immediately beneath the cellular layers (Durbin 1973, p. 790). On the other hand, one gets the impression that in soft tissues the transplutoniums, being more mobile, are somewhat more likely to appear in diffuse patterns, as contrasted to the polyatomic aggregates characteristic of insoluble plutonium salts. Several laboratories have shown this to be true generally. However, differences in chemical form and route of administration frequently mask differences among the elements. A start was made at Hanford on the metabolism of einsteinium and berkelium (Hungate et al. 1972; Smith 1972). The Utah group (Lloyd et al. 1974) checked out the behavior of curium in the beagle.

The Berkeley and Utah laboratories in this country and D. M. Taylor's laboratory in the United Kingdom have probably made the most extensive and organized autoradiographic studies on the transplutoniums, except for inhaled material, which has been dealt with at Hanford and Lovelace.

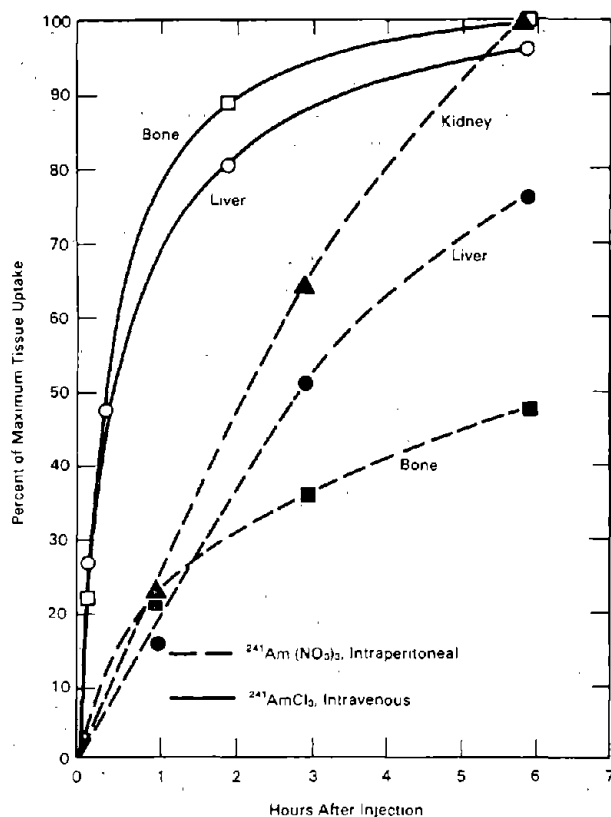


FIGURE 8.19. Accumulation of ^{241}Am in the skeleton, liver, and kidneys of rats after intravenous injection of $^{241}\text{AmCl}_3$, (Belyaev 1969) or intraperitoneal injection of $^{241}\text{Am}(\text{NO}_3)_3$ (Tseveleva and Yerokhin 1969). Data are expressed as percent of the maximum uptake in each tissue. (Redrawn from Durbin 1973, figure 18.21. Reprinted with permission of Springer-Verlag, Heidelberg, copyright 1973.)

3. Chemical Binding

D. M. Taylor (1973b) gives an excellent review of the chemical and physical properties of the transplutonium elements of interest in biology. He points out the deficiency of such information relative to plutonium and the problems of avoiding radiation effects in solutions of materials with such high specific activity. Nevertheless, he is able to extrapolate to the group as a whole from work on americium and curium, as well as the actual work on elements of higher atomic weight. He points out their lesser tendency to undergo hydrolytic reactions in solution, the great stability of the III valence state^(a) and, thus, lack of the many oxidation states seen with plutonium. But he emphasizes that complex formation and hydrolysis still play an important part in their solution chemistry. Binding to proteins either in vitro or in vivo seems to be less than with Pu (IV). As a result, these elements may be in several forms in vivo in contrast to the strong complex of plutonium with ferritin.

(a) Nobelium is unique in having valence II as the most stable oxidation state in solution.

Durbin takes the view that the rapid translocation of transplutonic nuclides from soft tissue to blood and then to bone indicates that they are not bound to cellular components, but exist rather in extracellular fluid (ECF). This may be true also in part for Pu (IV), but the stability of the Pu (IV) transferrin complex makes for much slower leakage of plutonium into ECF.^(a)

4. Excretion

Each laboratory has done its share toward furthering our knowledge of the excretion of the transplutonics. But the Berkeley data appear to be the most numerous and most completely studied, except for inhalation work, with Utah and Lovelace close behind. One problem is to be sure the administered levels are low enough to preclude radiation damage. Because of the early deposition in liver, much of the initial excretion is via bile to the gastrointestinal tract. This predicts a preponderance of excretion via the feces, and it is true in general. But contrasts abound. The amount of einsteinium in feces, for example, falls rapidly to about 0.1% of the dose per day at about twenty days, while the amount in urine, which is initially higher than the amount in feces, seems to level off at this same 0.1% per day. By contrast in the rat at least, ²⁴¹Am and ²⁴²Cm start with about 10% of the dose in urine at one day, with a maximum of around 3% in feces at ten days. But the urinary excretion rate falls precipitously to less than 0.02% per day by thirty days, while the fecal excretion rate is almost ten times as high at about 0.3% per day. Berkelium is like einsteinium, insofar as the few data available can tell. These contrasts in early excretion rates are illustrated in figure 8.20A and B (references are to the 1973 paper).

In some cases the feces-to-urine ratio would actually reverse as a function of time. It is unfortunate that the data for urinary excretion do not go beyond thirty-five days, probably because of the difficulties of measuring urine at such low concentrations. On the other hand, in the monkey, where longer-term studies were practical, the excretion of ²⁴¹Am citrate remained predominantly in feces, except in the first few days, out to over fifteen hundred days (Durbin 1973, figure 18.40). With ²³⁹Pu in adult beagles, the ratio feces/urine begins below 1 (about 0.6), goes to about 7 at three days, then gradually falls to a constant value of about 1.5 from thirty to five thousand days (Stover, Atherton, and Keller 1959). It will be remembered that the now classic Langham relations for plutonium excretion in man (chapter 7) put the fecal-to-urine ratio slightly greater than 1 during the first thirty days, while it becomes progressively smaller with time, being less than 1 for the bulk of the period up to at least five years. The difference between man and dog in plutonium excretion is not large, but between man and rat it is very large, with fecal excretion predominating in the rat.

Information of the type gathered is important for those instances where bioassay must depend upon excretion measurements. And the research on balance points to differences between plutonium and the transplutonic elements, with the fecal route more important for the transplutonics. But we have no long-term studies on man with the transplutonics to compare with those on plutonium.^(b) Thus, the generalization must be a cautious one.

(a) In her review, Durbin (figure 18.12) presents a kinetic model for initial transport and deposition of the trivalent elements with compartments for ECF-bound versus free, plasma-bound versus free, liver, bone, excreta, and soft tissues.

(b) The few long-term incidents we have are accidental intakes and were treated with chelating agents (see chapter 19).

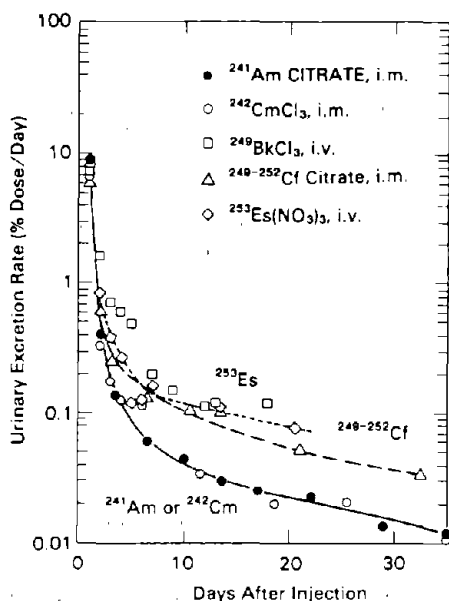


FIGURE 8.20A. Early excretion rates of trivalent actinide elements in the urine of the adult rat: ^{241}Am and $^{249-252}\text{Cf}$, Durbin, Jeung, and Williams (1969, 1972a,b); Durbin, Williams, and Jeung (1972); ^{242}Cm , Scott, Axelrod, and Hamilton (1949); ^{249}Bk , Hungate et al. (1972); ^{253}Es , V. H. Smith (1972). (Redrawn from Durbin 1973, p. 837. Reprinted with permission of Springer-Verlag, Heidelberg, copyright 1973.)

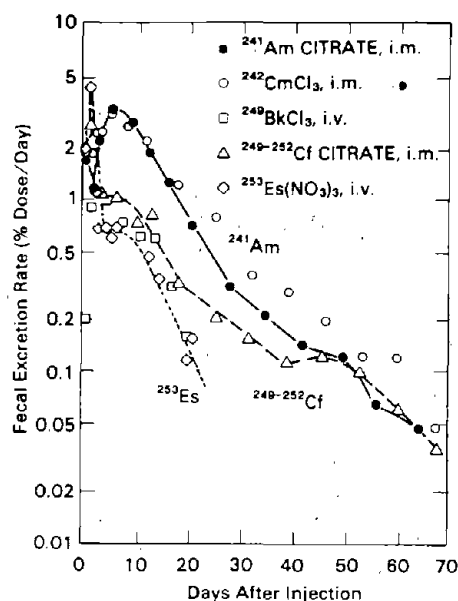


FIGURE 8.20B. Early rates of excretion of trivalent actinide elements in the feces of the adult rat. Data sources are the same as given in figure 8.20A. (Redrawn from Durbin 1973, p. 838. Reprinted with permission of Springer-Verlag, Heidelberg, copyright 1973.)

Fortunately, many of the transplutronics can be measured by means other than collection of excreta. Hence, the somewhat insecure footing provided by researches on excretion is not so serious a practical problem as it is a challenge to the understanding of mechanisms. While some work is continuing in this field, it has had to be curtailed by the needs in other areas, including chemical toxicology and environmental transport problems.

5. Addendum: Distribution and Retention

Recently, the group at New York University has published the results of several years of work on the metabolism of ^{243}Am and ^{244}Cm in the baboon (Lo Sasso, Cohen, and Wrenn 1981). In the discussion section, they present an interspecies comparison of americium and curium deposition and retention in liver. This is reproduced below as table 8.11.

It appears that the two elements, americium and curium, behave quite similarly in a given species, but differences among the species are large; the differences do not follow any obvious relationship to body weight. This interspecies problem does not appear to extend to bone.

TABLE 8.11. Interspecies Comparison of Actinide Deposition and Retention in Liver

Species	Route of Exposure	Chemical Form	²⁴³ Cm		²⁴¹ Am	
			Initial Deposition in Liver (% injected dose)	T _{1/2}	Initial Deposition in Liver (% injected dose)	T _{1/2}
Rat ^a	iv	Citrate or chloride	60	9.0 ± 0.3 days	57	7.5 ± 0.5 days
Dog ^b	iv	Citrate	35	~ years	50	~10 years
Baboon ^c	iv	Citrate	20	45 days	27	28 days
Cynomolgus monkey ^a	iv	Citrate	—	—	53	70 days

^a Deposition in liver = $L_{\max}(\%) = L_t + G.I._t + \sum Fe_t$, where L_t = amount of nuclide in liver at time t , $G.I._t$ = amount of nuclide in G.I. tract at time t , $\sum Fe_t$ = cumulative fecal excretion at time t .

^b Deposition in liver determined by combination of total-body and partial-body counting.

^c Deposition in liver determined by combination of total-body counting, cumulative fecal excretion, and liver biopsies.

Source: Modified slightly from Lo Sasso, Cohen, and Wrenn 1981. Reprinted with permission of Academic Press, Inc., Orlando, Florida, copyright 1981.

C. Toxicity

1. Acute Effects

The LD_{50/30} (lethal dose to 50% of the animals in thirty days) for ²⁴¹Am has been given by Zalikin, Moskalev, and Petrovich (1968) as 110 μ Ci/kg for rats. Durbin (1973, table 18.32) summarizes acute toxicity findings from Los Alamos, Chicago, Lovelace, and the Institute of Biophysics in Moscow for the three long-lived actinides. LD₅₀ values at 30, 60, 120 to 150, 250, and 300 to 350 days are quite similar for all three elements. The animals were adult and young rats and the Chinese hamster. Durbin (1973, table 18.33) also brings together the acute toxicity data for the dog using primarily work from Utah, Chicago, Lovelace, and Moscow. The information is sparse on the dog, since few investigators wish to expend valuable dogs in acute toxicity experiments when they might contribute information on long-term metabolism and effects. However, it appears that the same story applies to the transplutoniums as to plutonium: somewhat greater sensitivity in the dog by a factor of about two. The transplutoniums and plutonium are, on balance, not significantly different, at least in the dog.

Thus, the differences in deposition in soft tissues described in earlier paragraphs seem not to affect acute toxicity of the longer-lived transplutoniums compared to plutonium. Einsteinium, being both shorter lived and more rapidly excreted than americium or curium, is less toxic per activity unit (μ Ci) administered. Durbin estimates the LD_{50/30} in the rat as about 250 μ Ci/kg. The lack of difference in acute toxicity of these elements, despite significant differences in tissue distribution, recalls a point made by Stannard many years ago (Stannard

1956): there may be many occasions with elements depositing in several tissues when toxicity is better related to total body burden than to the burden in any single organ.

The effects earlier than sixty days with these large doses are referable primarily to bone marrow injury. Later deaths appeared to be referable to several organs. The most sensitive indicator of damage, as usual, is depression of the white cell count.

On the postulate that distribution of ^{144}Ce - ^{144}Pr is quite similar to that of plutonium, americium, and curium, Durbin used the acute toxicity as a way to compare the effectiveness of alpha emitters with beta emitters deposited in the body. The $\text{LD}_{50/30}$ averaged $100\ \mu\text{Ci/kg}$ for the alpha emitters in rats and was much smaller than the $1,830\ \mu\text{Ci/kg}$ for the beta-emitter pair ^{144}Ce - ^{144}Pr . In the dog, the figures were $35\ \mu\text{Ci/kg}$ versus $110\ \mu\text{Ci/kg}$. The difference between alphas and betas is clearly significant, with the alpha emitters, as always, the more effective. It is not difficult to explain why the ratio of effectiveness is smaller in the dog than in the rat. The range of the beta particles is likely to include much more bone and bone marrow in the dog and be dissipated more outside of bone and marrow in the rat.

Durbin points out that the relative effectiveness for bone marrow damage may be inversely related to body size.

2. Long-Term Effects

a. Bone Tumors

There is no doubt that the transplutronics can produce bone tumors. Indeed, osteogenic sarcomas appear to be the most sensitive effect produced by deposition of plutonium, americium, curium, and einsteinium in mice, rats, and dogs (Bair 1974). The Utah beagle experiment and the Russian work are the prime sources of information concerning parenteral administration to the dog. But the Utah work is even now not far enough along to support calculation of toxicity ratios to radium, which we examined in detail earlier for some other elements. We can only speculate that the relationship will resemble that for plutonium. Information after inhalation (details in chapter 9) comes primarily from PNL, Lovelace, and the USSR.

There is much more information on the rat, but it is not easy to sort out clear-cut evidence on whether or not the transplutronics are more efficient, less efficient, or about the same as plutonium in inducing bone tumors. The earliest postwar study in the rat was done by Langham and Carter (1951) with ^{241}Am . They gave 32 to $63\ \mu\text{Ci/kg}$. Six of thirty-two animals (19%) developed osteogenic sarcomas before 350 days. The associated radiation doses were 7,800 to 16,000 rad, not an indication of high efficiency of the transplutronics. Indeed, the administered dose was quite high, and life spans were short.

Later experiments detailed by Durbin showed similar percentages of bone tumors at much lower administered doses of ^{241}Am , e.g., $2.5\ \mu\text{Ci/kg}$ and $5.8\ \mu\text{Ci/kg}$ and associated radiation doses of 1,800 to 2,500 and 1,700 to 3,100 rad depending upon how long the animal lived.

David Taylor and his colleagues in the United Kingdom (e.g., Taylor and Bensted 1969; Bensted, Taylor, and Sowby 1965) found the rat to be significantly less sensitive to ^{241}Am than to ^{239}Pu in terms of bone-tumor development. The dose levels of ^{241}Am were 2.5 to $7\ \mu\text{Ci/kg}$ and were compared with $3\ \mu\text{Ci/kg}$ of ^{239}Pu , given intravenously. The americium doses produced 21% and 47% bone

tumors, respectively, while the plutonium dose produced an 80% incidence. There were soft-tissue lesions, including leukemia, in all groups of rats, but these did not show the same relation to dose. The authors propose an explanation of the difference between the elements as follows:

1. Plutonium deposits much more heavily on endosteal surfaces than does americium.
2. Plutonium is bound quite strongly by bone sialoprotein. Binding of americium to it is weaker (preliminary observations).

The U.K. workers are fully convinced that americium is less effective than plutonium in producing bone tumors, but suggest going to still lower dosage levels that have less shortening of life span from other causes.

There is probably no real conflict between the U.K. conclusions and those from the Durbin summary. The latter considered a number of disparate experiments from many laboratories. The conclusion that americium is about equally effective as plutonium is probably conservative for the rat, but not for the dog. Obviously, we need not only more long-term information for americium, but much more complete studies for curium and the other transplutronics to be secure quantitatively, or to consider alteration of allowable intake.

b. Other Long-Term Effects

Inhaled actinides can produce lung cancer, but there may be a difference between transplutronics and plutonium. The greater mobility of the transplutronics may result in shorter residence time in lung and more deposition in skeleton. We will examine this question in chapter 9.

Bair (1974) proposes from studies in rats that ^{253}Es is less efficient than plutonium in producing lung cancer, but more efficient in producing bone cancer. The information was obtained from animals receiving the einsteinium by intratracheal instillation.

A very interesting finding in the dog is concentration of americium in the thyroid. This came largely from Utah work. G. Taylor et al. in a Utah annual report (Taylor et al. 1976) describe morphological changes in the thyroid in young beagles receiving 2.88, 0.91, or 0.296 $\mu\text{Ci/kg}$ of ^{241}Am . The percent of injected dose per kilogram of thyroid tissue varied from about 20 to over 100,^(a) higher than skeleton and only a little lower than liver (Lloyd et al. 1967; Atherton et al. 1968).

No symptoms of clinical thyroid deficiency have appeared even yet, but microscopic lesions such as fibrosis, loss of colloid, loss of follicular and increase of residual epithelium have all occurred. While no thyroid tumors have appeared, it is not unlikely that one or more will turn up if bone tumors do not interfere first.

Liver and kidney failure have been reported in the dogs. The occasionally noted tendency of americium to be lethal sooner than ^{239}Pu may be linked to such effects.

The usual radiation effects are seen on the components of circulating blood. All of the transplutronics are more effective than ^{226}Ra , with a curious special effectiveness of californium in reducing the leucocyte count. There has been considerable effort in the area of cytogenetic changes in the cells of liver and

(a) The weight of the thyroid in the beagle is, of course, never as much as a kilogram. Hence, depositions of over 100% on a kilogram basis are understandable.

bone marrow. These are summarized in Durbin's review. The work has continued, especially at Lovelace and in the USSR. While it is hard to equate frequency of chromosome aberrations to other manifestations of biological effect, intercomparisons for this effect are instructive. For example, the beta-emitter pair ^{144}Ce - ^{144}Pr produced about one-twentieth the effect produced by ^{241}Am or ^{252}Cf with no dose-rate dependence for the alpha emitters.

The aberration frequency for ^{252}Cf was lower on the basis of accumulated radiation dose than that for ^{241}Am , despite the fact that about 3% of the nuclear transformations of ^{252}Cf are spontaneous fission reactions. If the energy is calculated for the particles alone, then ^{241}Am and ^{252}Cf are about the same (Durbin review). The investigators (Brooks, McClellan, and McKay 1971; Brooks, Mewhinney, and McClellan 1972; and McKay, Brooks, and McClellan 1969) speculated that the fission fragments might have too short a range in the tissue to be scored in their system, or much of their energy was wasted because of their very high LET. But this finding should not be extrapolated to other effects of ^{252}Cf .

Effects of the transplutronics on growth and reproduction have been studied, especially at PNL and in the USSR. Again americium was the element most used. There seemed to be a threshold dose (less than $4\ \mu\text{Ci/kg}$) in the pregnant female below which implantations were normal, and rapidly increasing numbers of embryonic and intrauterine deaths occurred as the dose was increased. Apparently enough of these elements can pass the placenta to exert effects, even though, as we saw earlier, they do not cross easily.

Alterations in postnatal development of the offspring of ^{241}Am -injected female rats included slow development, depressed reproductive capacity, and some blood disorders.

3. Effective Toxicity

Toxic effects per se are not the only factor controlling the risk of a given element. As we shall see in chapters 15 and 16, metabolic behavior in the body and transfer in the environment may modify inherent toxicity. We can call the result "effective toxicity."

Stannard (1975b) compared the effective toxicity of the transuranics by calculating ratios of their maximum permissible concentrations to that of tritium. With oral intake, iodine and strontium are well ahead of uranium, ^{239}Pu or ^{241}Pu , and ^{247}Cm ; ^{233}U and ^{247}Cm are ahead of ^{239}Pu ; while ^{241}Am and ^{239}Pu are about the same. By contrast, the maximum allowable concentrations in air give plutonium the highest ratio against tritium (3.3×10^6). Americium is a factor of ten less. Both of these were with bone considered as critical organ. The ratio of plutonium to tritium is somewhat less when lung is the critical organ, but still very large (2×10^5).

4. Comment

It is important that current long-term toxicity studies with the transplutronics be carried to completion. There are still gaps in the picture—especially for the elements above americium. But it is also important that the pharmacodynamics in humans be understood well for the development of good metabolic models. We will look at these activities further in chapter 16.

VIII. Summary and Commentary

The three decades after World War II saw enormous efforts embracing the health aspects of radioactive materials. Much of it concerned their uses in diagnosis and therapy (see chapter 20), some of it concerned efforts at therapeutic removal of deposited radionuclides (see chapter 19). Much of the remainder focused on the untoward effects we had perforce to concentrate on in reviewing the wartime work. Some of the largest and longest experiments in the history of biomedicine were organized around extensions of the problems perceived in the 1940s. These included in-depth comparisons of the metabolism and effects of important radionuclides in "king-sized" experiments with beagles; multi-generational studies in sheep and swine; a modicum of work on primates; and an enormous investment of time, talent, and resources in definitive inhalation experiments. (The inhalation work is described separately in chapters 9 and 10.)

Although no large populations of humans were exposed, except to the fallout from weapons tests (chapter 12), there were a few metabolism experiments on patients in metabolic wards, and rather intensive study of a Los Alamos worker population that had been in areas of relatively high potential contamination during the war years. In addition, the workers at the Rocky Flats plutonium plant received special scrutiny along with the environment around the plant. No biological effects have yet been discovered in any of these populations that could be attributed clearly to exposure to plutonium or other actinides. This is rather remarkable when the opportunities for intake are considered. As Dr. Louis Hempelmann, who had much to do with the medical care of the Los Alamos workers, remarked, we can be thankful indeed that plutonium is much less soluble in the gut and less transportable than radium. Except for that, we might easily be now studying a population of exposed individuals with health effects comparable to those from radium.

The chapter begins with a review of postwar work at Argonne National Laboratory and the University of California at Berkeley. This added considerably to their wartime efforts. At Argonne, the largest effort involved completion of the relative toxicity comparisons in the mouse, considerable expansion of the characterization of pathology, and forays into possible cofactor mechanisms for carcinogenesis.

Next is a discussion of the systematic studies at Berkeley, doing what Dr. Patricia Durbin characterized as "chewing our way through the periodic table." Primary emphasis was on strontium, cesium, various lanthanons, and heavy metals. Also, the potential for astatine to supplement iodine in treatment of thyroid disorders was explored until it was clear that it offered no advantages. After the death of Joseph Hamilton, much of this work was carried forward by Dr. Durbin.

The development of the king-sized experiments at the University of Utah, the University of California at Davis, and the Lovelace Inhalation Toxicology Laboratory is traced in considerable detail. Results of the Utah work are examined, while those of the Davis and Lovelace projects are postponed for more appropriate later chapters. These major experiments, now approaching conclusion (1987) of their original objectives, added immeasurably to our knowledge of metabolism, effects, and mechanisms of action of the selected fission products and actinides. Yet, there is still work to be done, especially to follow up cues toward cancer mechanisms developed in the studies.

The postwar years at Hanford (PNL) saw a major study of iodine in sheep, of strontium in miniature swine and in pygmy goats (more in chapter 13), of

radionuclides in the juvenile and fetal mammal, of gastrointestinal tract absorption and effects, and some of the earliest definitive research on the behavior and effects of tritium in biological systems. Much of this is summarized in the many Hanford symposia, whose titles and references are given. Perhaps the greatest surprise was the lack of effect on reproductive performance or on the fetus of significant body burdens carried over several generations. Only when the mother's health deteriorated significantly were there clear effects in these areas.

Los Alamos was able to mount bona fide research with various fission products, the actinides, and tritium after being inhibited during the war years. This was in addition to the careful study of the Los Alamos worker group, the general population of Los Alamos, and the "hot particle" problem (see chapter 9). Among the key results of the Los Alamos work was a long series of reports by Chester Richmond and his colleagues on the comparative metabolism of radionuclides in mammals. As we will see in later chapters, Wright Langham, who brought infinite patience to the characterization of plutonium excretion in humans and animals, was identified with all aspects of plutonium biology to the extent that he was frequently regarded as "Mr. Plutonium" in postwar biomedical circles.

Work from many other quarters is added, including some of the work done abroad.

Since studies of the transplutonic elements were not concentrated in any single major experiment, the postwar work with these is drawn together as a separate section of the chapter. Here, the indefatigable efforts of Patricia Durbin in bringing together a scattered and disparate literature are especially evident. It appears that many of the transplutonics (e.g., americium) are more transportable than is plutonium, and may be even more effective. However, the returns are not yet in on this feature.

The appellation "Golden Era" may be quite appropriate for these major undertakings, especially when taken together with the inhalation work to be described presently.

Note added in proof: An important review of the several long-term dog experiments discussed in part in this chapter occurred at the twenty-second Hanford Life Sciences Symposium. This and a still more recent review by Thompson of the legacy of the experiments have been added to the summary of our knowledge in chapter 21.

**NOTE 1—Text of Statement by Dr. Walter Claus (AEC-ERDA)
at the Twenty-Fifth-Anniversary Symposium of the Utah Project**

One may well wonder, philosophically, what has been the chain of events that lie behind us—how we, you and you and I—happen to be here together tonight. I recently came into possession of an ancient scroll that seems so pertinent to this occasion that I would like to read to you a few of its passages on Genesis, for therein it is written:

In the beginning, there was only ignorance and darkness, broken but by the faint gleam of radium in Bob Evans' bone-pile, while in a fabled land far to the East there did exist, for one brief shining moment, a fleeting wisp of glory known as AEC/DBM. And there, upon a throne of gold sat the Great White Father, and the light from him did shine as the sun cast from a

thousand polished shields—and his name was Warren. And the Father turned to his noblest son, Bowers, who sat upon his right hand, and he said: "Go thou hence, John, and bring light unto the benighted." And John did, and he called upon his henchmen, Evans, and Brues, and Eisenbud, and Brandt, and Claus, and together with the Great White Father, they gathered in that big hostelry beneath the sign of the bee-hive, and enunciated the Dogma, that "as radium in man shall be unto radium in the dog, so shall plutonium in man be as plutonium in the dog." And the statistician proclaimed that the number of the dogs shall be as thirty in each group, and all proclaimed that the name of the dog shall be Beagle. Now these mighty words were hailed abroad as one giant leap for mankind—but they were a very small step for the Beagle.

And so there came to be, in this land of the bee-hive, a great colony of Beagles, and of men and women to succor them and to administer to their wants—Red Stover and Betsy Stover (Adam and Eve in this new world), Bob Bay, Marv Van Dilla, Jim Arnold, Webster Jee, Dave Atherton, Jean Dougherty and Garth Westenskow—and over all did Bowers, the Noblest, in his wisdom and benevolence, brood upon them.

And then again, in that mystic land far to the East, the Father turned to his tiniest son who sat far down upon his left hand, and he spake thus: "Go thou, Walter, and cause to fall upon our chosen ones a deluge of golden manna, but be not overly generous lest they desert the Dogma for the pursuit of ikons and glittering gadgets." And Walter did; and he caused his golden lyre to sing of the beauties of thrift and economy to Stover, the Red—but that young devil took the lyre and all!

And lo! the Colony took unto itself the name "Radiobiology Laboratory," and it thrived. But in that great land to the East, the father-figure of Warren became that of Bugher, and Bugher became Dunham, and Dunham became Totter, and Totter became Liverman; while the stewardship of Claus became that of Bruner, which became that of Carter and Wachholz. The AEC became ERDA, and DBM became DBER. In the Colony, the moving spirit of Bowers became that of Dougherty, and that of Dougherty became that of Jee; while only the Master-mind of Evans goes on, and on, and on!

But still the Colony thrived, even unto its twenty-fifth year, and it sent forth many emissaries into the Land of Science, and it produced myriads of learned facts and fancies, speeches and books, and publications in the journals of the world, and symposia and conferences and workshops—and wise men and women gathered there to give homage in the jargon of science and technology.

So end the passages in my scroll, and thus we see how it comes to pass that we are gathered here tonight—you and you and I.

Amen. (Claus 1976)

References

- Asling, C. W., J. G. Hamilton, D. Axelröd-Heller, and B. J. Louie. 1952. The localization of certain alkaline and rare earth elements in the costochondral junction of the rat. *Anat. Rec.* 113: 285-300.
- Asling, C. W., M. E. Johnston, P. W. Durbin, and J. G. Hamilton. 1957. *Localization of cerium-144 in the skeletal tissues of fetal rats*. UCRL-8024. Berkeley, Calif.: Univ. of Calif. Radiation Laboratory.

- Atherton, D. R., R. D. Lloyd, G. N. Taylor, B. J. Stover, and C. W. Mays. 1968. Distribution of ^{241}Am in the beagle. In *Research in radiobiology. Annual report of work in progress in the Internal Irradiation Program*. COO-119-237, pp. 117-23. Salt Lake City: Univ. of Utah.
- Bair, W. J. 1974. The biological effects of transuranium elements in experimental animals. In *Plutonium and other transuranium elements: Sources, environmental distribution and biomedical effects*. WASH-1359, pp. 171-241. Springfield, Va: National Technical Information Service. [Also Hearings of U.S. Environmental Protection Agency, vol. 1, USEPA, ORP/CSD-75-1, Washington, D.C.]
- Bair, W. J., D. H. Willard, I. C. Nelson, and A. C. Case. 1974. Comparative distribution and excretion of ^{237}Pu and ^{239}Pu nitrates in beagle dogs. *Health Phys.* 27:392-96.
- Ballou, J. E. 1958. Effects of age and mode of ingestion on absorption of plutonium. *Proc. Soc. Exp. Biol. and Med.* 98:726-27.
- Ballou, J. E., L. A. George II, and R. C. Thompson. 1962. The combined toxic effects of plutonium plus x-ray in rats. *Health Phys.* 8:581-87.
- Ballou, J. E., G. E. Dagle, K. E. McDonald, and R. L. Buschbom. 1977. Influence of inhaled Ca-DTPA on the long-term effects of inhaled Pu nitrate. *Health Phys.* 32:479-87.
- Belyaev, Yu. A. 1969. Americium-241 distribution in rats and the effect of complexing substances on its elimination. In *Radioaktivnye Izotopy i Organizm*, ed. Yu. I. Moskalov. Moscow: Izdatel'stvo Meditsina. [Translation to English: *Radioactive isotopes and the body*, AEC-tr-7195, pp. 168-74.]
- Bensted, J. P. M., D. M. Taylor, and F. D. Sowby. 1965. The carcinogenic effects of americium 241 and plutonium 239 in the rat. *Br. J. Radiol.* 38:920-25.
- Bistline, R. W., R. L. Watters, and J. L. Lebel. 1972. A study of translocation dynamics of plutonium and americium from simulated puncture wounds in beagle dogs. *Health Phys.* 22:829-31.
- Blair, H. A. 1968. Radiation dose-time relations for induction of bone tumors in the dog and skin tumors in the rat. *Radiat. Res.* 34:501-22.
- Brooks, A. L. 1975. Chromosome damage in liver cells from low dose rate alpha, beta, and gamma irradiation: Derivation of RBE. *Science* 190:1090-92.
- Brooks, A. L., R. O. McClellan, and L. R. McKay. 1971. The relative biological effectiveness of alpha, beta and gamma irradiation in producing metaphase chromosome aberrations *in vivo* in Chinese hamster liver cells. *Radiat. Res.* 47:332-33.
- Brooks, A. L., J. A. Mewhinney, and R. O. McClellan. 1972. The *in vivo* cytogenetic effects of ^{252}Cf on liver and bone marrow of the Chinese hamster. *Health Phys.* 22:701-06.
- Brues, A. M. 1949. Biological hazards and toxicity of radioactive isotopes. *J. Clin. Invest.* 28:1286-96.
- Brues, A. M., H. Auerbach, G. DeRoche, and D. D. Grube. 1966-1969. Mechanisms of carcinogenesis. In *Biological and Medical Research Division annual reports for 1966, 1967, 1968, and 1969*. ANL-7278, 7409, 7535, and 7635. Argonne, Ill.: Argonne National Laboratory.
- Brues, A. M., H. Auerbach, D. Grube, and G. DeRoche. 1967. Studies on soft-tissue dosage from strontium-90. In Lenihan, Loutit, and Martin 1967, pp. 207-12.
- Buldakov, L. A., E. R. Lyubchanskii, Yu. I. Moskalov, and A. P. Nifatov. 1970. *Problems of plutonium toxicology*. Originally issued by Atom Publications, Moscow, 1969. Translated by A. A. Horvath. [Edited as Report LF-tr-41 by R. G. Thomas and issued as a report from Lovelace Foundation for Medical Education and Research, Albuquerque, New Mexico.]
- Bustad, L. K., ed. 1963. The biology of radioiodine. Proceedings of the 2d annual Hanford biology symposium held in Richland, Wash., June 17-19, 1963. *Health Phys.* 9:1081-1426.
- Bustad, L. K. and R. O. McClellan, eds. 1966. *Swine in biomedical research*. Proceedings of the 5th annual Hanford biology symposium held in Richland, Wash., July 19-22, 1965. Richland, Wash.: Pacific Northwest Laboratory.
- Bustad, L. K., W. J. Clarke, L. A. George II, V. G. Horstman, R. O. McClellan, R. L. Persing, L. J. Seigneur, and J. L. Terry. 1962. Preliminary observations on metabolism and toxicity of plutonium in miniature swine. *Health Phys.* 8:615-20.

- Bustad, L. K., L. A. George, Jr., S. Marks, D. E. Warner, C. M. Barnes, K. E. Herde, and H. A. Kornberg. 1957. Biological effects of ^{137}Cs continuously administered to sheep. *Radiat. Res.* 6:380-413. [A supplemental paper to the regular issue prepared to give detailed material in a single place. With a foreword by H. M. Parker.]
- Bustad, L. K., K. A. Stitzel, E. K. Haro, and M. Goldman. 1972. The choice of the beagle for radiobiologic studies. In *Radiobiology of plutonium*, eds. B. J. Stover and W. S. S. Jee, pp. 203-11. Salt Lake City: The J. W. Press.
- Cable, J. W., V. G. Horstman, W. J. Clarke, and L. K. Bustad. 1962. Effects of intradermal injections of plutonium in swine. *Health Phys.* 8:629-34.
- Casarett, G. W. 1973. Pathogenesis of radionuclide-induced tumors. In *Radionuclide carcinogenesis*, eds. C. L. Sanders, R. H. Busch, J. E. Ballou, and D. D. Mahlum, CONF-720505, pp. 1-14. Proceedings of the 12th annual Hanford biology symposium held in Richland, Wash., May 10-12, 1972. Springfield, Va.: National Technical Information Service.
- Casarett, G. W., L. W. Tuttle, and R. C. Baxter. 1962. Pathology of imbibed Sr^{90} in rats and monkeys. In Dougherty et al. 1962a, pp. 329-36.
- Casarett, G. W., J. Conley, B. J. Henderson, and L. W. Tuttle. 1958. Late pathologic effects of imbibed Sr^{90} in bones of rats. *Radiat. Res.* 9:100.
- Clarke, W. J. 1962. Comparative histopathology of Pu^{239} , Ra^{226} and Sr^{90} in pig bone. *Health Phys.* 8:621-27.
- Claus, W. D. 1976. Genesis. In *Health effects of plutonium and radium*, ed. W. S. S. Jee, pp. xiii-xiv. Salt Lake City: J. W. Press.
- Cohen, N. and M. E. Wrenn. 1973. Metabolic characteristics of ^{241}Am in the adult baboon. *Radiat. Res.* 55:129-43.
- Decker, C. F., L. V. Kaspar, and W. P. Norris. 1964. The variation of strontium metabolism with age in the dog. *Radiat. Res.* 23:475-90.
- Decker, C. F. and W. P. Norris. 1959. *The retention of strontium-85 in the dog*. ANL-6200, pp. 78-81. Argonne, Ill.: Argonne National Laboratory.
- Della Rosa, R. J., F. A. Smith, and J. N. Stannard. 1961. The renal excretion of strontium and calcium in dogs. *Int. J. Radiat. Biol. & Relat. Stud. Phys. Chem. & Med.* 3:557-78.
- Dougherty, J. H. 1971. Early hematologic effects of californium in the beagle. In *Research in radiobiology. Annual report of work in progress in the Internal Irradiation Program*. COO-119-244, pp. 117-25. Salt Lake City: Univ. of Utah.
- Dougherty, J. H. and L. S. Rosenblatt. 1971. Long-term hematological effects of internal emitters in beagles. *Radiat. Res.* 48:319-31.
- Dougherty, T. F., W. S. S. Jee, C. W. Mays, and B. J. Stover, eds. 1962a. *Some aspects of internal irradiation*. Proceedings of a symposium held in Heber, Utah, May 8-11, 1961. New York-Oxford: Pergamon Press.
- Dougherty, T. F., B. J. Stover, J. H. Dougherty, W. S. S. Jee, C. W. Mays, C. E. Rehfeld, W. R. Christensen, and H. C. Goldthorpe. 1962b. Studies of the biological effects of Ra^{226} , Pu^{239} , $\text{Ra}^{226}(\text{MsTh}_1)$, $\text{Th}^{228}(\text{RdTh})$, and Sr^{90} in adult beagles. *Radiat. Res.* 17:625-81.
- Durbin, P. W. 1960. Metabolic characteristics within a chemical family. *Health Phys.* 2:225-38.
- Durbin, P. W. 1962. Distribution of the transuranic elements in mammals. *Health Phys.* 8:665-71.
- Durbin, P. W. 1971. *Plutonium in man: A twenty-five year review*. UCRL-20850. Berkeley, Calif.: Lawrence Radiation Laboratory.
- Durbin, P. W. 1972. Plutonium in man: A new look at the old data. Chapter 7.2 in *Radiobiology of plutonium*, eds. B. J. Stover and W. S. S. Jee, pp. 469-530. Salt Lake City: The J. W. Press.
- Durbin, P. W. 1973. Metabolism and biological effects of the transplutonium elements. Chapter 18 in *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh, pp. 739-896. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.
- Durbin, P. W. 1974a. *Behavior of plutonium in animals and man*. Paper presented at a plutonium information meeting for an ad hoc subcommittee of the advisory-committee on reactor safeguards. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.

- Durbin, P. W. 1974b. *Transfer of plutonium from soil to plants: A review of the problem*. UCID-3689.
- Durbin, P. W. 1975. Plutonium in mammals: Influence of plutonium chemistry, route of administration, and physiological status of the animal on initial distribution and long-term metabolism. *Health Phys.* 29:495-510.
- Durbin, P. W. 1976. What was going on at Crocker Laboratory when I landed there as a dishwasher and animal tender. Paper presented at the 21st annual meeting of the Health Physics Society held in San Francisco, July 1976. [Typescript from tape and slides kindly supplied by R. L. Kathren, Richland, Wash.]
- Durbin, P. W. 1978a. Actinide biological research in progress, 1976-1977. In *Research needs in actinide biology*, CONF-770491, Appendix B. Proceedings of a workshop held in Seattle, Wash., April 5-7, 1977. Springfield, Va.: National Technical Information Service.
- Durbin, P. W. 1978b. A summary of actinide biological research, 1943-1977. In *Research needs in actinide biology*, CONF-770491, Appendix A. Proceedings of a workshop held in Seattle, Wash., April 5-7, 1977. Springfield, Va.: National Technical Information Service.
- Durbin, P. W., M. W. Horovitz, and E. R. Close. 1972. Plutonium deposition kinetics in the rat. *Health Phys.* 22:731-41.
- Durbin, P. W., N. Jeung, and M. H. Williams. 1969. Dynamics of ^{241}Am in the skeleton of the rat: A study of the relationship between behavior of bone-seeking elements and bone-growth status. In *Delayed effects of bone-seeking radionuclides*, eds. C. W. Mays, W. S. S. Jee, R. D. Lloyd, B. J. Stover, J. H. Dougherty, and G. N. Taylor, pp. 137-56. Salt Lake City: Univ. of Utah Press.
- Durbin, P. W., N. Jeung, and M. H. Williams. 1972a. Distribution, retention, and excretion of ^{241}Am in adult female rats and monkeys. [Unpublished.]
- Durbin, P. W., N. Jeung and M. H. Williams. 1972b. Distribution, retention, and excretion of $^{249}\text{-}^{252}\text{Cf}$ in adult female rats. [Unpublished.]
- Durbin, P. and H. Jones. 1958. Estimation of the 'turnover' equation of strontium-90 for human bones. In *Proceedings of the 2d United Nations international conference on the peaceful uses of atomic energy*, vol. 23, pp. 140-41. Held in Geneva, September 1-13, 1958. Geneva: United Nations.
- Durbin, P. W., J. G. Scott, and J. G. Hamilton. 1957. *The distribution of radioisotopes of some heavy metals in the rat*. UCRL-3607. Berkeley, Calif.: Lawrence Radiation Laboratory.
- Durbin, P. W., M. H. Williams, and N. Jeung. 1961. Metabolism of americium-241 in the monkey. *Radiat. Res.* 14:462.
- Durbin, P. W., M. H. Williams, and N. Jeung. 1972. Long-term excretion of $^{241}\text{-americium}$ by the cynomolgus monkey. *Health Phys.* 23:417-18.
- Durbin, P. W. and M. E. Wrenn. 1975. Metabolism and effects of uranium in animals. In *Conference on occupational health experience with uranium*, ERDA-93, pp. 67-129. Held in Arlington, Va., April 28-30, 1975. Washington, D.C.: Energy Research and Development Administration.
- Durbin, P. W., C. W. Asling, N. Jeung, M. H. Williams, J. Post, M. E. Johnston, and J. G. Hamilton. 1958. *The metabolism and toxicity of radium-223 in rats*. UCRL-8189. Berkeley, Calif.: Lawrence Radiation Laboratory.
- Durbin, P. W., C. W. Asling, M. E. Johnston, J. G. Hamilton, and M. H. Williams, with technical assistance of N. Jeung, M. W. Parrott, and R. H. Newman. 1956a. The metabolism of the lanthanones in the rat. II. Live studies of the tissue deposition of intravenously administered radioisotopes. In *Rare earths in biochemical and medical research*, eds. G. C. Kyker and E. B. Anderson, ORINS-12, pp. 171-92. Proceedings of an ORINS conference, October 1955. Oak Ridge, Tenn.: Oak Ridge Institute of Nuclear Studies, Medical Div.
- Durbin, P. W., C. W. Asling, M. E. Johnston, J. G. Hamilton, and M. H. Williams. 1956b. UCRL companion report to 1956 paper in *Rare earth symposium*. UCRL-3191. Berkeley, Calif.: Lawrence Radiation Laboratory.

- Durbin, P. W., N. Jeung, M. H. Williams, and M. W. Parrott. 1973. Long-term metabolism of ^{90}Sr in rhesus monkeys (*Macaca mulatta*). In *Proceedings of the 3d international conference of the International Radiation Protection Association*, ed. W. S. Snyder, CONF-730907-P2, pp. 1412-17. Held in Washington, D.C. September 9-14, 1973. Oak Ridge, Tenn.: Technical Information Center.
- Durbin, P. W., M. W. Parrott, M. H. Williams, M. E. Johnston, W. Asling, and J. G. Hamilton. 1956c. Metabolic studies with strontium-90 in the rhesus monkey (preliminary report). In *The shorter-term biological hazards of a fallout field*, eds. G. M. Dunning and J. A. Hilcken, pp. 173-83. Proceedings of a symposium held in Washington, D.C., December 1956. Washington, D.C.: Atomic Energy Commission.
- Durbin, P. W., M. W. Parrott, M. H. Williams, M. E. Johnston, W. Asling, and J. G. Hamilton. 1957. *Metabolic studies with strontium-90 in the rhesus monkey* (preliminary report). UCRL-3634. Berkeley, Calif.: Lawrence Radiation Laboratory.
- Durbin, P. W., M. H. Williams, M. Gee, R. H. Newman, and J. G. Hamilton. 1955. *The metabolism of the lanthanons in the rat*. UCRL-3066. Berkeley, Calif.: Lawrence Radiation Laboratory.
- Durbin, P. W., M. H. Williams, M. Gee, R. H. Newman, and J. G. Hamilton. 1956d. Metabolism of the lanthanons in the rat. *Proc. Soc. Exp. Biol. Med.* 91:78-85.
- Durbin, P. W., M. H. Williams, M. W. Parrott, and H. B. Jones. 1959. Retention of Sr^{90} and Ca^{45} in rhesus monkeys. *Radiology* 72:98-99.
- Finkel, M. P. 1956. Relative biological effectiveness of internal emitters. *Radiology* 67:665-72.
- Finkel, M. P. 1959a. Induction of tumors with internally administered isotopes. In *Radiation Biology and Cancer*, pp. 322-35. Austin.: Univ. of Tex. Press.
- Finkel, M. P. 1959b. Late effects of internally deposited radioisotopes in laboratory animals. *Radiat. Res. Suppl.* 1:265-79.
- Finkel, M. P. 1978, 1981. Personal interviews.
- Finkel, M. P., P. J. Bergstrand, and B. O. Biskis. 1960. The consequences of the continuous ingestion of Sr^{90} by mice. *Radiology* 74:458-67.
- Finkel, M. P., P. J. Bergstrand, and B. O. Biskis. 1961. The latent period, incidence, and growth of Sr^{90} -induced osteosarcomas in CF1 and CBA Mice. *Radiology* 77:269-81.
- Finkel, M. P. and B. O. Biskis. 1962. Toxicity of plutonium in mice. *Health Phys.* 8:565-79.
- Finkel, M. P., B. O. Biskis, and P. J. Bergstrand. 1960. Radioisotope toxicity: Significance of chronic administration. In *Radioisotopes in the biosphere*, eds. R. S. Caldecott and L. A. Snyder, pp. 461-73. Proceedings of a symposium held in Minneapolis, Minn. Minneapolis: Univ. of Minn., Center for Continuation Study.
- Finkel, M. P., B. O. Biskis, and P. B. Jinkins. 1969. Toxicity of radium-226 in mice. In *Radiation-induced cancer*, pp. 369-91. Proceedings of a symposium held in Athens, April 28-May 2, 1969. Vienna: International Atomic Energy Agency.
- Finkel, M. P., B. O. Biskis, and G. M. Scribner. 1959. The influence of strontium-90 upon life span and neoplasms of mice. In *Progress in nuclear energy*, eds. J. G. Bugher, J. Coursaget, and J. F. Loutit, ser. VI, vol. 2, Biological sciences, pp. 199-209. New York-Oxford: Pergamon Press.
- Finkel, M. P., A. M. Brues, and H. Lisco. 1952. *Toxicity of Sr^{89} in mice: Design of experiment and survival following single injection*. ANL-4840, pp. 57-62. Argonne, Ill.: Argonne National Laboratory.
- Finkel, M. P., A. M. Brues, and H. Lisco. 1954. *The toxicity of Sr^{89} in mice*. ANL-5247, pp. 25-29. Argonne, Ill.: Argonne National Laboratory.
- Finkel, M. P., P. B. Jinkins, and B. O. Biskis. 1964. Parameters of radiation dosage that influence production of osteogenic sarcomas in mice. Paper presented at an international symposium on the control of cell division and the induction of cancer, held at Lima, Peru, and Cali, Columbia. *Nat. Cancer Inst. Monogr.* 14:243-70.
- Finkel, M. P. and W. E. Kisielski. 1976. Plutonium incorporation through ingestion by young animals. In *The health effects of plutonium and radium*, ed. W. S. S. Jee, pp. 57-69. Salt Lake City: The J. W. Press.

- Finkel, M. P., H. Lisco, and A. M. Brues. 1954. *The toxicity of Sr⁸⁹ in mice: Tumors among the control animals*. ANL-5288, pp. 23-34. Argonne, Ill.: Argonne National Laboratory.
- Finkel, M. P., H. Lisco, and A. M. Brues. 1955. *Toxicity of Sr⁸⁹ in mice: Malignant bone tumors*. ANL-5378. Argonne, Ill.: Argonne National Laboratory.
- Finkel, M. P., B. O. Biskis, I. Greco, and R. W. Camden. 1972. Strontium-90 toxicity in dogs: Status of Argonne study on influence of age and dosage pattern. In Goldman and Bustad 1972, pp. 285-312.
- Finkel, M. P., H. Lisco, K. A. Lathrop, and A. M. Brues. 1956. *Toxicity of locally deposited yttrium-91 in mice. I. Experimental design and gross pathology*. ANL-5655, pp. 39-46. Argonne, Ill.: Argonne National Laboratory.
- Foreman, H. 1962. Studies on the mechanism of plutonium uptake by bone. *Health Phys.* 8:713-16.
- Foreman, H., W. Moss, and W. Langham. 1960. Plutonium accumulation from long-term occupational exposure. *Health Phys.* 2:326-33.
- Furchner, J. E. 1957. Relative biological effectiveness of tritium beta-particles and Co⁶⁰ gamma-rays measured by lethality in CFI mice. *Radiat. Res.* 6:483-90.
- Furchner, J. E. and G. A. Drake. 1971. Comparative metabolism of radionuclides in mammals—VI. Retention of ⁹⁵Nb in the mouse, rat, monkey, and dog. *Health Phys.* 21:173-80.
- Furchner, J. E. and G. A. Drake. 1976. Comparative metabolism of radionuclides in mammals—XI. Retention of ¹¹³Sn in the mouse, rat, monkey, and dog. *Health Phys.* 31:219-24.
- Furchner, J. E., J. E. London, and J. S. Wilson. 1975. Comparative metabolism of radionuclides in mammals—IX. Retention of ⁷⁵Se in the mouse, rat, monkey, and dog. *Health Phys.* 29:641-48.
- Furchner, J. E. and C. R. Richmond. 1963. Comparative metabolism of radioisotopes in mammals—II. Retention of iodine¹³¹ by four mammalian species. *Health Phys.* 9:277-82.
- Furchner, J. E., C. R. Richmond, and G. A. Drake. 1966. Comparative metabolism of radionuclides in mammals—III. Retention of manganese-54 in the mouse, rat, monkey, and dog. *Health Phys.* 12:1415-23.
- Furchner, J. E., C. R. Richmond, and G. A. Drake. 1968. Comparative metabolism of radionuclides in mammals—IV. Retention of silver-110_m in the mouse, rat, monkey, and dog. *Health Phys.* 15:505-14.
- Furchner, J. E., C. R. Richmond, and G. A. Drake. 1971a. Comparative metabolism of radionuclides in mammals—V. Retention of ¹⁹²Ir in the mouse, rat, monkey, and dog. *Health Phys.* 20:375-82.
- Furchner, J. E., C. R. Richmond, and G. A. Drake. 1971b. Comparative metabolism of radionuclides in mammals—VII. Retention of ¹⁰⁶Ru in the mouse, rat, monkey, and dog. *Health Phys.* 21:355-65.
- Furchner, J. E., C. R. Richmond, and J. E. London. 1973. Comparative metabolism of radionuclides in mammals. VIII. Retention of beryllium in the mouse, rat, monkey, and dog. *Health Phys.* 24:293-300.
- Goldman, M. D. 1980. Personal interview, December 5, 1980.
- Goldman, M. and L. K. Bustad. 1972. *Biomedical implications of radiostrontium exposure*. Proceedings of a symposium held at Davis, Calif., February 22-24, 1971. CONF-710201. Springfield, Va.: National Technical Information Service.
- Gomez, L. S., J. L. Lebel, and R. L. Watters. 1972. The effect of lymph node removal on PuO₂ translocation. *Health Phys.* 22: 833-36.
- Grahn, D., B. H. Frystak, C. H. Lee, J. J. Russell, and A. Lindenbaum. 1979. Dominant lethal mutations and chromosome aberrations induced in male mice by incorporated ²³⁹Pu and by external fission neutron and gamma irradiation. In *Biological implications of radionuclides released from nuclear industries*, vol. I, pp. 163-84. Proceedings of a symposium held in Vienna, March 26-30, 1979. Vienna: International Atomic Energy Agency.
- Hamilton, J. G. 1954. *The metabolic properties of various materials*, UCRL-2661, pp. 23, 25-27. Berkeley, Calif.: Lawrence Radiation Laboratory.

- Hanford Biology Annual Reports—1951: HW-25021, April 15, 1952. 1953: HW-30437. 1954: HW-35917, January 3, 1955. 1955: HW-41500, February 16, 1956. 1956: HW-47500, January 4, 1957. 1961: HW-72500, January 1962. 1966: BNWL-480, vol. 1, July 1967. 1971: BNWL-1650, pt. 1, September 1972. 1973: BNWL-1850, pt. 1, August 1974. 1974: BNWL-1950, pt. 1, March 1975.
- Healy, J. W. 1957. Estimation of plutonium lung burden by urine analysis. *Am. Ind. Hyg. Assoc. Q.* 18:261-66.
- Healy, J. W., ed. 1975. Plutonium—Health implications for man. Proceedings of the 2d Los Alamos life sciences symposium, held at Los Alamos, N. Mex., May 22-24, 1974. *Health Phys.* 29:441-632.
- Horstman, V. G., W. J. Clarke, P. L. Hackett, M. E. Kerr, R. L. Persing, and L. K. Bustad. 1960. Anatomical and physiological data in miniature swine. In *Hanford biology research, annual report for 1959*. HW-65500, pp. 59-67. Richland, Wash: Hanford Works.
- Hungate, F. P., J. E. Ballou, D. D. Mahlum, M. Kashima, V. H. Smith, C. L. Sanders, D. W. Baxter, M. R. Sikov, and R. C. Thompson. 1972. Preliminary data on ^{253}Es and ^{249}Bk metabolism in rats. *Health Phys.* 22:653-56.
- Jee, W. S. S. and J. S. Arnold. 1960. Radioisotopes in the teeth of dogs—I. The distribution of plutonium, radium, radiothorium, mesothorium and strontium and the sequence of histopathologic changes in teeth containing plutonium. *Arch. Oral Biol.* 2:215-38.
- Jee, W. S. S., R. B. Dell, and M. A. Davis. 1971. Autoradiographic study of the early distribution of ^{45}Ca in alveolar bone of dogs. In *Research in radiobiology. Annual report of work in progress in the Internal Irradiation Program*. COO-119-244, pp. 270-83. Salt Lake City: Univ. of Utah.
- Jee, W. S. S., J. S. Arnold, T. H. Cochran, J. A. Twente, and R. S. Mical. 1962. Relationship of microdistribution of alpha particles to damage. In Dougherty et al. 1962a, pp. 27-45.
- Jee, W. S. S., D. R. Atherton, F. Bruenger, J. H. Dougherty, R. D. Lloyd, C. W. Mays, C. J. Nabors, Jr., W. Stevens, B. J. Stover, G. N. Taylor, and L. A. Woodbury. 1975. Current status of Utah long-term ^{239}Pu studies. In *Biological and environmental effects of low-level radiation*, STI/PUB/409, vol. 2, pp. 79-94. Proceedings of a symposium held in Chicago, November 3-7, 1975. Vienna: International Atomic Energy Agency.
- Jee, W. S. S., M. H. Bartley, N. L. Dockum, J. Yee, and G. H. Kenner. 1969. Vascular changes in bones following bone-seeking radionuclides. In *Delayed effects of bone-seeking radionuclides*, eds. C. W. Mays, W. S. S. Jee, R. D. Lloyd, B. J. Stover, J. H. Dougherty, and G. N. Taylor, pp. 437-55. Salt Lake City: Univ. of Utah Press.
- Johnson, L. J. and R. L. Watters. 1970. Relative distribution of plutonium and americium following experimental PuO_2 implants. *Health Phys.* 19:743-49.
- Katz, J. 1951. *Plutonium metabolism: A literature review*. HW-21868. Richland, Wash.: Hanford Works.
- Katz, J., H. A. Kornberg, and H. M. Parker. 1955. Absorption of plutonium fed chronically to rats. I. Fraction deposited in skeleton and soft tissues following oral administration of solutions of very low mass concentration. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* 73:303-08.
- Langham, W. H. 1957. Excretion methods. The application of excretion analyses to the determination of body burden of radioactive isotopes. *Br. J. Radiol. Suppl.* 7, pt. V, pp. 95-113.
- Langham, W. H. 1959. Physiology and toxicology of plutonium-239 and its industrial medical control. *Health Phys.* 2:172-85.
- Langham, W. H. 1964. Physiological properties of plutonium and assessment of body burden in man. In *Assessment of radioactivity in man*, vol. 2, pp. 565-81. Proceedings of a symposium held in Heidelberg, May 11-16, 1964. Vienna: International Atomic Energy Agency.
- Langham, W. H. 1972. The biological implications of the transuranium elements for man. *Health Phys.* 22:943-52.
- Langham, W. H. and R. E. Carter. 1951. *The relative physiological and toxicological properties of americium and plutonium*. LA-1309. Univ. of Calif.: Los Alamos Scientific Laboratory.

- Langham, W. H., J. N. P. Lawrence, J. McClelland, and L. H. Hempelmann. 1962. The Los Alamos Scientific Laboratory's experience with plutonium in man. *Health Phys.* 8:753-60.
- Lebel, J. L., E. H. Bull, L. J. Johnson, and R. L. Watters. 1970. Lymphosarcoma associated with nodal concentration of plutonium in dogs: A preliminary report. *Am. J. Vet. Res.* 31:1513-16.
- Lenihan, J. M. A., J. F. Loutit, and J. H. Martin, eds. 1967. *Strontium metabolism*. Proceedings of an international symposium held in Chapel Cross, Glasgow and Strontian, Scotland, May 5-7, 1966. London-New York: Academic Press.
- Lloyd, E. 1968. Comparison of the relative rates of transfer of barium, radium, and strontium between blood and bone. *Annual report*, ANL-7489, pp. 77-81. Argonne, Ill., Argonne National Laboratory.
- Lloyd, R. D., ed. 1970. *Retention and dosimetry of some injected radionuclides in beagles*. COO-119-241, Radiobiology division of the department of anatomy. Salt Lake City: Univ. of Utah.
- Lloyd, R. D., D. R. Atherton, C. W. Mays, S. S. McFarland, and J. L. Williams. 1974. The early excretion, retention and distribution of injected curium citrate in beagles. *Health Phys.* 27:61-67.
- Lloyd, R. D., C. W. Mays, D. R. Atherton, G. N. Taylor, and M. A. Van Dilla. 1976. Retention and skeletal dosimetry of injected ^{226}Ra , ^{228}Ra , and ^{90}Sr in beagles. *Radiat. Res.* 66:274-87.
- Lloyd, R. D., C. W. Mays, D. R. Atherton, G. N. Taylor, and J. L. Williams. 1971. *Californium retention, excretion and distribution in beagles soon after injection*. COO-119-244, pp. 102-16, Radiobiology division of the department of anatomy. Salt Lake City: Univ. of Utah.
- Lloyd, R. D., C. W. Mays, G. N. Taylor, D. R. Atherton, and L. R. Shabestari. 1967. Retention of injected ^{241}Am in beagles. *Health Phys.* 13:938 (abstract).
- Lo Sasso, T., N. Cohen, and M. E. Wrenn. 1981. Distribution and retention of ^{243}Am and ^{244}Cm in the adult baboon. *Radiat. Res.* 85:173-83.
- Loutit, J. F. 1962. *Irradiation of mice and men*. Chicago, Ill.: Univ. of Chicago Press.
- Mahlum, D. D., and M. R. Sikov. 1974. Distribution and toxicity of monomeric and polymeric ^{239}Pu in immature and adult rats. *Radiat. Res.* 60:75-88.
- Marshall, J. H. and M. P. Finkel. 1960. *Autoradiographic dosimetry of mouse bones containing Ca^{45} , Sr^{90} or Ra^{226} . II. The sensitive region in the induction of osteogenic sarcomas*. ANL-6199, pp. 44-54. Argonne, Ill.: Argonne National Laboratory.
- Marshall, J. H., R. E. Rowland, and J. Jowsey. 1956. *Quantitative autoradiographic measurement of calcium-45 concentrations in cortical bone*. ANL-5679, pp. 48-62. Argonne, Ill.: Argonne National Laboratory.
- Mays, C. W. 1958. Determination of localized alpha-dose. I. With particular emphasis on plutonium. In *Annual report*, COO-217, pp. 161-80. Salt Lake City: Univ. of Utah.
- Mays, C. W. 1960. Determination of localized alpha-dose. II. From alpha-emitters-buried in mineralized bone. In *Annual report*, COO-220, pp. 200-06. Salt Lake City: Univ. of Utah.
- Mays, C. W. and M. P. Finkel. 1980. RBE of α -particles versus β -particles in bone sarcoma induction. In *Radiation protection: A systematic approach to safety*, vol. 2, pp. 401-5. Proceedings of the 5th congress of the International Radiation Protection Association held in Jerusalem, March 9-14, 1980. Oxford: Pergamon Press.
- Mays, C. W., R. D. Lloyd, and D. R. Atherton. 1974. Transuranic elements in gonadal tissue. In *Research in radiobiology. Annual report of work in progress in the Internal Irradiation Program*. COO-119-249, pp. 308-10. Salt Lake City: Univ. of Utah.
- Mays, C. W. and K. A. Sears. 1962. Determination of localized alpha-dose. III. From surface and volume deposits of Pu^{239} , Th^{228} , and Ra^{226} . In *Semi-annual report*, COO-226, pp. 78-85. Salt Lake City: Univ. of Utah.
- Mays, C. W. and A. B. Tueller. 1964. Determination of localized alpha-dose. IV. In soft tissue near radioactive bone. In *Semi-annual report*, COO-119-229, pp. 199-205. Salt Lake City: Univ. of Utah.

- Mays, C. W., T. F. Dougherty, G. N. Taylor, R. D. Lloyd, B. J. Stover, W. S. S. Jee, W. R. Christensen, J. H. Dougherty, and D. R. Atherton. 1969. Radiation-induced bone cancer in beagles. In *Delayed effects of bone-seeking radionuclides*, eds. C. W. Mays, W. S. S. Jee, R. D. Lloyd, B. J. Stover, J. H. Dougherty, and G. N. Taylor, pp. 387-408. Salt Lake City: Univ. of Utah Press.
- Mays, C. W., W. S. S. Jee, C. J. Nabors, Jr., G. N. Taylor, W. Stevens, J. Dougherty, W. R. Christensen, and T. F. Dougherty. 1973. Some scientific advantages in the use of the beagle in long term radiobiological studies. In *Research in radiobiology. Annual report of work in progress in the Internal Irradiation Program*. COO-119-248, pp. 110-40. Salt Lake City: Univ. of Utah.
- Mays, C. W., G. N. Taylor, W. Stevens, W. S. S. Jee, and M. E. Wrenn. 1979. Bone sarcomas at low doses of α -radiation in beagles. In *Research in radiobiology. Annual report of work in progress in the Internal Irradiation Program*. COO-119-254, pp. 9-14. Salt Lake City: Univ. of Utah.
- McKay, L. R., A. L. Brooks, and R. O. McClellan. 1969. Metabolism and toxicity of ^{241}Am in the Chinese hamster. In *Fission Product Inhalation Program annual report*, LF-41, pp. 203-08. Albuquerque, N. Mex.: Lovelace Foundation for Medical Education and Research.
- NAS-FRC. See National Academy of Science-Federal Radiation Council.
- National Academy of Science-Federal Radiation Council. 1964. *Implications to man of irradiation by internally deposited strontium-89, strontium-90, and cesium-137*. Washington, D.C.: Federal Radiation Council. [Arthur C. Upton, committee chairman.]
- National Council on Radiation Protection and Measurements. 1975. *Krypton-85 in the atmosphere—Accumulation, biological significance and control technology*. Report no. 44. Washington, D.C.
- National Council on Radiation Protection and Measurements. 1976. *Tritium measurement techniques*. Report no. 47. Washington, D.C.
- National Council on Radiation Protection and Measurements. 1977. *Cesium-137 from the environment to man: Metabolism and dose*. Report no. 52. Washington, D.C.
- National Council on Radiation Protection and Measurements. 1978. *Physical, chemical, and biological properties of radiocerium relevant to radiation protection guidelines*. Report no. 60. Washington, D.C.
- National Council on Radiation Protection and Measurements. 1979. *Tritium and other radionuclide labeled organic compounds incorporated in genetic material*. Report no. 63. Washington, D.C.
- NCRP. See National Council on Radiation Protection and Measurements.
- Norwood, W. D. 1956. Treatment of plutonium poisoning with zirconium citrate and with Ca EDTA. In *Meeting on therapy of radioelement poisoning held October 20-21, 1955*. ANL-5584; pp. 36-44. Argonne, Ill.: Argonne National Laboratory.
- Parker, H. M. 1973. Plutonium. Industrial hygiene, health physics and related aspects. Chapter 14 in *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, J. B. Hursh, pp. 613-67. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.
- Pinson, E. A., E. C. Anderson, and V. Lotz. 1952. *The specific activity of tritium in the organic components of the skin and fat of man following eight months chronic exposure to HTO in body fluids*. LAMS-2946, pp. 84-85. Los Alamos, N. Mex.: Univ. of Calif.: Los Alamos Scientific Laboratory.
- Pinson, E. A. and W. H. Langham. 1957. Physiology and toxicology of tritium in man. *J. Appl. Physiol.* 10:108-26. Reprinted as a landmark paper in *Health Phys.* 38:1087-1110.
- Redman, H. C., A. J. Wilson, S. W. Bielfelt, and R. O. McClellan. 1970. Beagle dog production experience at the fission product inhalation program (1961-1968). *Lab. Anim. Care* 20:61-68.
- Rehfeld, C. E., J. A. Blomquist, and G. N. Taylor. 1972. The beagles. In *Radiobiology of plutonium*, eds. B. J. Stover and W. S. S. Jee, pp. 47-57. Salt Lake City: The J. W. Press.
- Richmond, C. R. 1979. Personal interview, taped April 18, 1979.

- Richmond, C. R., J. Langham, and R. S. Stone. 1970. Biological response to small discrete highly radioactive sources. II. Morphogenesis of microlesions in rat lungs from intravenously injected $^{238}\text{PuO}_2$ microspheres. *Health Phys.* 18:401-08.
- Richmond, C. R. and J. E. London. 1968. Long-term retention of cobalt-60 by rats. LA-3848, p. 84. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Richmond, C. R., J. E. London, and J. E. Furchner. 1964. Metabolism of radiocesium by man and selected laboratory mammals. *Radiat. Res.* 22:226-27. [abstract]
- Richmond, C. R. and R. L. Thomas. 1975. Plutonium and other actinide elements in gonadal tissue of man and animals. *Health Phys.* 29:241-50.
- Richmond, C. R., J. E. Furchner, G. A. Trafton, and W. H. Langham. 1962. Comparative metabolism of radionuclides in mammals—I. Uptake and retention of orally administered Zn^{65} by four mammalian species. *Health Phys.* 8:481-89.
- Richmond, C. R., W. H. Langham, J. S. Wilson, and J. E. London. 1968. Protracted feeding of plutonium-238 microspheres to beagles. I. Macro- and microscopic observations of the gastrointestinal tract and estimates of deposition in liver, spleen, and lymph nodes. In *Biological and medical research group (H-4) of the health division annual report, July 1966 through June 1977*. LA-3848, pp. 80-83. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Rowland, R. E. and P. W. Durbin. 1976. Survival, causes of death, and estimated tissue doses in a group of human beings injected with plutonium. In *The health effects of plutonium and radium*, ed. W. S. S. Jee, pp. 329-41. Salt Lake City: The J. W. Press.
- Rowland, R. E. and J. H. Marshall. 1959. Calibration of the quantitative alpha-track autoradiographic technique. ANL-6049, pp. 23-29. Argonne, Ill.: Argonne National Laboratory.
- Russell, W. L., R. B. Cumming, E. M. Kelly, and A. Lindenbaum. 1978. Plutonium-induced specific-locus mutations in mice. [Abstract in *Genetics* 88 (Suppl. 4:S85).]
- Sacher, G. A. 1954. *The lethality function for exponentially decaying exposures; Applications to the toxicity of tritium*. ANL-5288. Argonne, Ill.: Argonne National Laboratory.
- Schubert, J., M. P. Finkel, M. R. White, and G. M. Hirsch. 1950. Plutonium and yttrium content of the blood, liver, and skeleton of the rat at different times after intravenous administration. *J. Biol. Chem.* 182:635-42.
- Schweitzer, G. K. and M. Jackson. 1952. Radiocolloids. *J. Chem. Educ.* 29:513-22.
- Scott, K. G., D. J. Axelrod, and J. G. Hamilton. 1949. The metabolism of curium in the rat. *J. Biol. Chem.* 177:325-35.
- Seaborg, G. T. 1973. Medical uses: Americium-241; californium-252. Chapter 21 in *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh, pp. 929-40. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.
- Sears, K. A., W. S. S. Jee, and C. W. Mays. 1962. Radium dosimetry. In *Semi-annual report*, COO-226, pp. 86-94. Salt Lake City: Univ. of Utah.
- Shipman, T. L. 1969. H division activities. Manuscript of paper presented at laboratory information meeting, May 6, 1969. [Kindly supplied by Dr. George Voelz.]
- Sikov, M. R. 1979. Personal interview, June 6, 1979.
- Sikov, M. R. and D. D. Mahlum, eds. 1969. *Radiation biology of the fetal and juvenile mammal*, CONF-690501. Proceedings of the 9th annual Hanford biology symposium held in Richland, Wash., May 5-8, 1969. Springfield, Va.: National Technical Information Service.
- Sikov, M. R. and D. D. Mahlum. 1972. Plutonium in the developing animal. *Health Phys.* 22:707-12.
- Sikov, M. R., V. H. Smith, and D. D. Mahlum. 1975. Teratologic effectiveness and fetal toxicity of DTPA in the rat. In *Pacific Northwest Laboratory annual report for 1974 to the USAEC Division of Biomedical and Environmental Research, Part 1, Biomedical sciences*. BNWL-1950, pt. 1, pp. 138-40. Richland, Wash.: Battelle, Pacific Northwest Laboratories.

- Smith, V. H. 1972. The biological disposition of $\text{Es}(\text{NO}_3)_3$ in rats after intravenous, intramuscular, subcutaneous, and transcutaneous administration. In *Pacific Northwest Laboratory annual report for 1971 to the USAEC Division of Biology and Medicine, Vol. 1, Life Sciences, Part 1, Biological sciences*. BNWL-1650, pt. 1, pp. 279-83. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Smith, V. H. 1979. Personal interview, taped June 7, 1979.
- Smith, J. M., D. R. Atherton, T. J. Wronski, and W. S. S. Jee. 1977. ^{239}Pu standards for quantitative neutron-induced autoradiography. In *Research in radiobiology. Annual report of work in progress in the Internal Irradiation Program*. COO-119-252, pp. 162-71. Salt Lake City: Univ. of Utah.
- Snyder, W. S., M. R. Ford, and G. G. Warner. 1968. The use of excretion data to predict the systemic body burden of plutonium. In *Diagnosis and treatment of deposited radionuclides*, eds. H. A. Kornberg and W. D. Norwood, pp. 279-90. Proceedings of the 7th annual Hanford biology symposium held in Richland, Wash., May 15-17, 1967. Amsterdam: Excerpta Medica Foundation.
- Speckman, T. W. and W. P. Norris. 1964. The age-dependence of strontium retention in rats and mice. *Radiat. Res.* 23:461-74.
- Stannard, J. N. 1956. Is the concept of "critical organ" valid in determining the maximum permissible level for exposure to radioactive materials? In *Proceedings of the international conference on the peaceful uses of atomic energy*, vol. 13, pp. 205-09. Held in Geneva, August 8-20, 1955, New York: United Nations.
- Stannard, J. N. 1973. Toxicology of radionuclides. *Annu. Rev. Pharmacol.* 13:325-57.
- Stannard, J. N. 1975a. The concepts of critical organ and radiation dose as applied to plutonium. *Health Phys.* 29:539-50.
- Stannard, J. N. 1975b. Toxicity of the transuranium elements with special emphasis on plutonium. In *Health and Safety Laboratory environmental quarterly report*, HASL-291, pt. I, pp. 19-32. New York: Energy Research Development Administration.
- Stannard, J. N., H. A. Blair, and R. C. Baxter. 1964. Mortality, life span, and growth of rats with a maintained body burden of polonium. *Radiat. Res. Suppl.* 5: 228-45.
- Stevens, W. and F. W. Bruenger. 1971a. Intracellular distribution of ^{249}Cf in canine liver. In *Research in radiobiology. Annual report of work in progress in the Internal Irradiation Program*. COO-119-244, pp. 149-50. Salt Lake City: Univ. of Utah.
- Stevens, W. and F. W. Bruenger. 1971b. The disappearance of californium-249 and californium-252 from the blood of beagles. In *Research in radiobiology. Annual report of work in progress in the Internal Irradiation Program*. COO-119-244, pp. 147-48. Salt Lake City: Univ. of Utah.
- Storer, J. B., P. S. Harris, J. E. Furchner, and W. H. Langham. 1957. The relative biological effectiveness of various ionizing radiations in mammalian systems. *Radiat. Res.* 6:188-288.
- Stover, B. J. 1976. $^{239}\text{Pu}(\text{IV})$: Skeletal dosimetry in the beagle. In *Health effects of plutonium and radium*, ed. W. S. S. Jee, pp. 97-103. Salt Lake City: The J. W. Press.
- Stover, B. J. 1980. Personal interview, December 7, 1980.
- Stover, B. J., D. R. Atherton, and N. Keller. 1959. Metabolism of Pu^{239} in adult beagle dogs. *Radiat. Res.* 10:130-47.
- Stover, B. J., D. R. Atherton, and C. W. Mays. 1962. Studies of the retention and distribution of Ra^{226} , Pu^{239} , Ra^{228} , (MsTh_3), Th^{228} , (RdTh), and Sr^{90} in adult beagles. In Dougherty et al. 1962a, pp. 7-25.
- Stover, B. J. and C. N. Stover, Jr. 1972. The laboratory for radiobiology at the Univ. of Utah. In *Radiobiology of plutonium*, eds. B. J. Stover and W. S. S. Jee, pp. 29-46. Salt Lake City: The J. W. Press.
- Sullivan, M. F., ed. 1968. *Gastrointestinal radiation injury*. Proceedings of the 6th annual Hanford biology symposium held in Richland, Wash., September 25-28, 1966. Amsterdam: Excerpta Medica Foundation.
- Sullivan, M. F. 1979. Taped personal interview, Richland, Wash., June 6, 1979.
- Sullivan, M. F. 1980. Absorption of actinide elements from the gastrointestinal tract of neonatal animals. *Health Phys.* 38:173-85.

- Sullivan, M. F., T. R. Garland, D. A. Cataldo, R. E. Wildung, and H. Drucker. 1980. Absorption of plutonium from the gastrointestinal tract of rats and guinea pigs after ingestion of alfalfa containing ^{238}Pu . *Health Phys.* 38:215-21.
- Taylor, D. M. 1973a. Chemical and physical properties of plutonium. Chapter 9 in *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh, pp. 323-47. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.
- Taylor, D. M. 1973b. Chemical and physical properties of the transplutonium elements. Chapter 17 in *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh, pp. 717-38. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.
- Taylor, D. M. and J. P. M. Bensted. 1969. Long-term biological damage from plutonium-239 and americium-241 in rats. In *Delayed effects of bone-seeking radionuclides*, eds. C. W. Mays, W. S. S. Jee, R. D. Lloyd, B. J. Stover, J. H. Dougherty, and G. N. Taylor, pp. 357-70. Salt Lake City: Univ. of Utah Press.
- Taylor, G. N. 1965. The use of therapy in experimental animals. In *Research in radiobiology. Annual report of work in progress in the Internal Irradiation Program*. COO-119-232, pp. 65-67. Salt Lake City: Univ. of Utah.
- Taylor, G. N., W. R. Christensen, W. S. S. Jee, and C. E. Rehfeld. 1962. *Gingival ulceration in beagles induced by Ra-226, Ra-228 or Th-228*. COO-226, pp. 35-41. Salt Lake City: Univ. of Utah.
- Taylor, G. N., T. F. Dougherty, L. Shabestari, and J. H. Dougherty. 1969a. Soft-tissue tumors in internally irradiated beagles. In *Delayed effects of bone-seeking radionuclides*, eds. C. W. Mays, W. S. S. Jee, R. D. Lloyd, B. J. Stover, J. H. Dougherty, and G. N. Taylor, pp. 323-36. Salt Lake City: Univ. of Utah Press.
- Taylor, G. N., W. S. S. Jee, R. B. Dell, C. W. Mays, J. L. Williams, and L. Shabestari. 1971. Distribution of californium-249 and berkelium-249 in the soft tissues of beagles. In *Research in radiobiology. Annual report of work in progress in the Internal Irradiation Program*. COO-119-244, pp. 126-46. Salt Lake City: Univ. of Utah.
- Taylor, G. N., W. S. S. Jee, J. L. Williams, B. Burggraff, and W. Angus. 1969b. Microscopic distribution of ^{241}Am in the beagle. In *Research in radiobiology. Annual report of work in progress in the Internal Irradiation Program*. COO-119-240, pp. 97-118. Salt Lake City: Univ. of Utah.
- Taylor, G. N., C. E. Rehfeld, K. W. Crook, and W. Fisher. 1961. The rate of tooth loss in beagles injected with Pu^{239} , Ra^{226} and Ra^{228} . In *Semi-annual report*, COO-224, pp. 32-37. Salt Lake City: Univ. of Utah.
- Taylor, G. N., I. Zizumbo, W. Angus, A. Jones, and D. Elliot. 1976. ^{241}Am induced thyroid lesions in the beagle—Interim observations. In *Research in radiobiology. Annual report of work in progress in the Internal Irradiation Program*. COO-119-251, pp. 144-66. Salt Lake City: Univ. of Utah.
- Thomas, R. G., J. E. Furchner, J. E. London, G. A. Drake, J. S. Wilson, and C. R. Richmond. 1976. Comparative metabolism of radionuclides in mammals—X. Retention of tracer-level cobalt in the mouse, rat, monkey, and dog. *Health Phys.* 31:323-33.
- Thompson, R. C. 1952. Studies of metabolic turnover with tritium as a tracer. I. Gross studies on the mouse. *J. Biol. Chem.* 197:81-87.
- Thompson, R. C. 1953. Studies of metabolic turnover with tritium as a tracer. II. Gross studies on the rat. *J. Biol. Chem.* 200:731-43.
- Thompson, R. C. 1954. Biological applications of tritium. *Nucleonics* 12(9):31-35.
- Thompson, R. C. 1956. *Research at Hanford on therapy for internally deposited plutonium*. Paper presented at a meeting on therapy of radioelement poisoning, October 20-21, 1955. ANL-5584, pp. 114-22. Argonne, Ill.: Argonne National Laboratory.
- Thompson, R. C. 1967. Biological factors. Chapter 23 in *Plutonium handbook: A guide to the technology*, ed. O. J. Wick, vol. 2, pp. 785-829. New York: Gordon & Breach.

- Thompson, R. C. 1971. *Review of laboratory animal experiments related to the radiobiology of tritium*. BNWL-SA-3739. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Thompson, R. C. 1973. *Biology of the transuranium elements. A bibliography*, BNWL-1782. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Thompson, R. C. 1976. *Biology of the transuranium elements. An indexed bibliography*. BNWL-2056. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Thompson, R. C. and J. E. Ballou. 1954. Studies of metabolic turnover with tritium as a tracer. IV. Metabolically inert lipid and protein fractions from the rat. *J. Biol. Chem.* 208:883-88.
- Totter, J. R. 1972. Biological research with plutonium 1944-1984. In *Radiobiology of plutonium*, eds. B. J. Stover and W. S. S. Jee, pp. 23-27. Salt Lake City: The J. W. Press.
- Trujillo, T. T., E. C. Anderson, and W. H. Langham. 1955. *Biological effects of inhalation of high concentrations of tritium gas*. LA-1986. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Tseveleva, I. A. and R. A. Yerokhin. 1969. Behavior of americium-241 in the body of rats under intraperitoneal and intratracheal administration. In *Radioaktivnye Izotopy i Organizm*, ed. Yu. I. Moskalev. Moscow: Izdatel'sto Meditsina. Translation to English, AEC-tr-7195, pp. 161-68.
- Tuttle, L. W., R. C. Baxter, M. Goldman, and W. F. Bale. 1959. *The metabolism and toxicology of Sr⁹⁰ in the rat: Rationale, experimental procedures, pilot experiments*. UR-424. Rochester, N. Y. Univ. of Rochester.
- Vaughan, J. in collaboration with B. Bleaney and D. M. Taylor. 1973. Distribution, excretion and effects of plutonium as a bone-seeker. Chapter 10 In *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh, pp. 349-502. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.
- Watters, R. L. and J. L. Lebel. 1972. Progress in the beagle studies at Colorado State Univ. *Health Phys.* 22:811-814.
- Weeks, M. H., J. Katz, W. D. Oakley, J. E. Ballou, L. A. George, L. K. Bustad, R. C. Thompson, and H. A. Kornberg. 1956. Further studies on the gastrointestinal absorption of plutonium. *Radiat. Res.* 4:339-47.
- Whitson, W. S. and W. S. S. Jee. 1971. Electron microscopy of radiation damage in bone. In *Research in radiobiology. Annual report of work in progress in the Internal Irradiation Program*. COO-119-244, pp. 250-53. Salt Lake City: Univ. of Utah.
- Woodard, H. Q. 1970. *The biological effects of tritium*. HASL-229. New York: U.S. Atomic Energy Commission, Health and Safety Laboratory.
- Woodward, K. T., C. R. Richmond, and W. Langham. 1956. Measurement of retention and excretion of radioisotopes of the alkali metals by mice and rats using an annular liquid scintillation counter. Paper from unpublished proceedings of the Health Physics Society, June 1956.
- Zalikin, G. A., Yu. I. Moskalev, and I. K. Petrovich. 1968. Distribution and biological effects of americium-241. *Radiobiologiya* 8:107-18. Translation to English, AEC-tr-6950.

Preface to Section III Inhalation Toxicology

Primary concern for health effects of radionuclides centered, until very recently, on their potential inhalation in the work place. In the early decades of the twentieth century, occupational exposures in the "dusty trades" had left a dismal trail of death and incapacitation due to effects of the inhaled dust on the respiratory system. A respectable start had been made toward measurement and control by the new specialty called industrial hygiene. Also, a modicum of research with animals inhaling chemicals of various degrees of toxicity had developed during the late 1920s and the 1930s.

The handling of uranium ore as one of the earliest major jobs of the new atomic energy industry proved also to be a dusty operation. The perceived health problem was again inhalation. Hence, a major effort was devoted to the inhalation toxicology of natural uranium. We have already seen one such experiment in chapter 2. There was much more, as we shall see presently.

It was a relatively small jump from inhalation experiments with chemically toxic substances to a low-specific-activity radionuclide mixture such as natural uranium. The basic apparatus and the control procedures could be developed without undue concern for contamination of the laboratory or operating personnel. Study of the more highly radioactive substances, whether natural or manmade, posed quite different problems. The prospect of purposely producing an aerosol of moderate to high radioactivity thoroughly frightened both administrators and potential investigators. Yet, as the work of World War II progressed, the need to know at least the behavior on inhalation, if not the effects, of the new radionuclides became more and more strident. It was not even known whether or not the presence of radioactivity would so change the charge characteristics of inhaled aerosols that information on distribution and excretion gained with stable isotopes would be inapplicable. Nor was there any good information on how to classify the lung and its accessory structures with regard to their radiosensitivity.

Therefore, during World War II, in addition to the inhalation work with uranium and thorium, there were a few forays into exposures to airborne polonium, plutonium, and the fission products. Obviously, dust feeds and the usual techniques for radioactively inert substances would not do. Instead, small experiments were designed in which the radioelement was volatilized from a hot wire or other small-scale devices. These provided some information on metabolic

behavior of inhaled radionuclides and confirmed the suspicion that there could be no surrogate for actual inhalation exposures. However, they gave no information on biological effects—especially the nagging problems of lung cancer. Such was urgently needed.

Fortunately, the almost absolute containment of radioelements within the “dry boxes” used for machining of uranium and plutonium, developed during World War II, encouraged early postwar investigators to apply the technique to experiments with aerosols of radionuclides. Also, much had been learned about aerosols and how to handle them and of the effect of particle size on retention and subsequent behavior. The work was expensive and laborious since all active systems needed to be at reduced pressure, and very efficient filter systems needed to be interposed at the final outlet. Also, the services of an aerosol physicist were essential for a successful program. As a result, there could not be very many laboratories engaged in such work. There developed a few major centers that specialized in the biomedical work with radioactive aerosols.

The chapters in this section describe the work during World War II and then the development of and results from the major centers that sprang up after the war and are, with one exception, still extremely active. The results have confirmed many times over the need for an actual inhalation experiment. Plutonium, for example, proved to be a potent producer of lung cancer on inhalation, despite the fact that the work described in section II, chapters 7 and 8, linked it primarily to bone cancer.

It must be concluded that because of the interest and dedication of the workers concerned and the continued support of federal agencies, the inhalation toxicology of radioactive materials has led the way for all of inhalation toxicology. It is hoped that these chapters illustrate the concepts, the techniques, and the principal results.

For convenience, work with substances that behave primarily as particles has been gathered in chapter 9. Substances that behave primarily as gases are discussed together in chapter 10.

The theoretical cutoff date (1980) for comprehensive inclusion of material in this book was advanced somewhat for these chapters because of the vigorous activity in the field. Nevertheless, only work of special importance or concern done in the early 1980s could be included in this already lengthy discussion.

OUTLINE

INHALATION TOXICOLOGY—A SPECIAL ENTITY

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system is in a transient state.

Capsule Chronology

- 1920s and 1930s** Work on toxic gases in laboratories of physiology, pharmacology, and toxicology, public health, industrial medicine, and mine safety on both sides of the Atlantic.
- 1930s–early 1940s** Development of aerosol science, advanced especially by invention of the electron microscope.
- 1940** Warren and Gates. Radiation pneumonitis described.

PERIOD OF WORLD WAR II

- 1943** Model experiment at Berkeley on airborne fission products (Hamilton and W. Cohn).
Preliminary investigation of airborne products from Chicago cyclotron (E. Tomkins).
- 1943–1947** Inhalation experiments with natural uranium at Rochester. Extensive studies on three-shift-a-day basis. Many species, compounds, acute, subacute, and chronic levels of exposure. Much correlative work on aerosols, design of exposure chambers, role of particle size. Reported primarily in National Nuclear Energy Series volumes in 1949 and 1951 (Voegtlin and Hodge).
- 1944** Metabolism and effects of short-lived airborne fission products using the Clinton "Pile" (Lanz and Teresi at Chicago). Work begins at Berkeley on aerosolized products of uranium bombardment at cyclotron (Hamilton and Scott).
- 1944–1945** Animals exposed to off-gases from Clinton "pile," mostly fission products (Scott et al. at Berkeley).
Chamber exposures with arcs and sparks, as well as sprays. Fission products and plutonium. Work at Berkeley (Scott et al.).
Extensive autoradiographic work with both the aerosols themselves and the animal recipients. Clear that insoluble complexes form in the lung and that inhalation picture is not the same as after intratracheal instillation (Berkeley). Some of the work not written up until after the war.
- 1944–1946** Work by Abrams at Chicago (Met Lab). Consistent efforts to develop aerosol technology. Methods devised for a wide variety of radionuclides. Both metabolism and effects studied. Larger quantities used than at Berkeley.
- 1944–1947** Inhalation work with rats at Rochester using ^{210}Po (Kimball and Fink). Aerosols administered by burning wire technique or nasal cannulation. Distribution different from after intravenous administration. Published in NNEs^(a) volume in 1950 (Fink).
- 1945** Acute toxicity of inhaled ^{144}Ce , also ruthenium (Abrams at Chicago). Tracer work begins on inhaled plutonium. Noted that it remains in lung for long periods (Abrams at Chicago).

(a) For abbreviations and acronyms, see Appendix D.

- 1946 Major summaries of Chicago work on inhalation of longer-lived fission products, also intubated and inhaled plutonium in rats (Abrams et al.).
High effectiveness of plutonium in producing lung damage hinted at by intubation work.
- 1948 Bloom reports on histopathological effects of inhaled radionuclides. Work done during the war (Chicago).

POST-WORLD WAR II

- 1949 First two volumes of Rochester uranium work published.
- 1949 et seq. Expansion of work on relation of particle size to toxicity, mostly at Rochester.
- 1949–1952 Follow-up at Berkeley of autoradiographic work done during war.
- 1950 Rochester experiments with inhaled polonium published.
Aerosol science becomes a separate entity at some projects.
- Early 1950 Studies at Hanford begin using intratracheal intubation.
- 1950s Inhalation work, mostly fission products and radon, at Naval Radiological Defense Laboratory (Cohn, Gong, and colleagues).
HASL, then NYU, work on inhalation problems in industry, mostly uranium (Eisenbud and Harley).
Studies by Herman Cember at University of Pittsburgh. Mostly insufflation and implanted radioactive beads. In 1960, Cember moves to Kettering Laboratory in Cincinnati and continues inhalation work.
- Mid-1950s Inhalation work begins in earnest at Hanford (Bair and colleagues).
- 1951 Second two volumes of Rochester uranium work published—emphasis on chronic effects. AEC Air Cleaning Conferences begin, continue through 1980.
- 1952 Radioactive Inhalation Section (Alpha Laboratory) organized at Rochester. Broad studies of retention, distribution, and, later, effects. Polonium-210, plutonium, radon, and daughters (see chapter 3) (Berke, L. Casarett, Mercer, Morken, Morrow, Scott, Smith, Stannard, Thomas, and Wilson).
Marinelli studies transport of radium in lung of man (ANL, Chicago).
- 1955 Lung cancer reported at Hanford from instilled plutonium (Wager).
- 1955 et seq. Long-term inhalation experiment with uranium at Rochester (Leach, Hodge, et al.).
NYU work on deposition and clearance of radioactive dust (Albert, Lippmann, and Laskin).
- 1955–1964 Polonium exposure of dogs and rats at Rochester.
- 1957 Lung cancer produced in rat by ^{210}Po (Rochester).
- 1958 Plutonium inhalation exposures begin at Rochester.
Malignant lung tumors appear in animals at Hanford receiving ruthenium dioxide by inhalation (Bair, Willard, et al.).
NYU work on implanted sources in lung.

- 1958-1961** Iodine inhalation work at Hanford (Bair and Willard).
Reports from Oak Ridge on inhalation of uranium aerosols by animals and man.
- 1959** Aerosol deposition studied in humans using sodium chloride (Morrow, et al. at Rochester).
- 1960s-1970s** Inhalation work at Hanford/Pacific Northwest Laboratory begins to concentrate on plutonium and radon + daughters. Long-term effectiveness of plutonium in producing lung cancer made clear (Bair, Park, et al.).
- 1960-1964** Lovelace Foundation Fission Product Inhalation Laboratory organized and facilities built (later called Inhalation Toxicology Research Institute). Early exposures limited to small animals. First dog exposed in 1964. Cesium-137 used. Soon followed by ^{91}Y , ^{144}Ce , and ^{90}Sr , all in both soluble and insoluble forms. Idea of using fused aluminosilicate particles as carriers for insoluble aerosols developed (White, Mercer, Thomas, Lie; later McClellan, Boecker, et al.).
- 1960-1964** Definitive reviews from Rochester on deposition and clearance mechanisms (Morrow and Casarett).
- 1960s through 1970s** Inhalation program at Wayne State University. Mixtures of stable and radioactive aerosols, rare earth elements (Vorwald and Berke).
- 1964** Air pollution by radioactive materials from fossil fuel plants described (Eisenbud, NYU).
SNAP-9 enters the atmosphere with 17 kilocuries of ^{238}Pu released. Much work and discussion of possible inhalation hazards from such sources.
Hanford biology symposium on Inhaled Radioactive Particles and Gases (Bair et al.).
Inhalation problems enunciated and studied in depth around projects such as SNAP, ROVER, Kiwi, and NERVA.^(a)
- Mid-1960s** Oak Ridge cooperative program with National Cancer Institute. Effect of external radiation on clearance and behavior of inhaled stable aerosols.
- 1965** Lovelace directed to place primary emphasis on the dog and include longevity studies.
- 1966** ICRP Task Group Lung Model published (Morrow et al.).
- Late 1960s** Sanders's work begins on peritoneal macrophage and plutonium. Expanded to pulmonary macrophage in subsequent years (Battelle).
- 1970** Differences in metabolism and effects between ^{238}Pu and ^{239}Pu established clearly (Stuart, Bair, et al., Battelle).
Relationship worked out between inhaled dose of plutonium and long-term incidence of lung cancer (Bair, Thompson, et al., Battelle).
- 1970s** Comparison of single and repeated inhalation exposures at Lovelace indicates real differences (Boecker).
Much lung modeling everywhere.

(a) See text for definitions.

- 1970s Use of whole-body counting begins for study of pulmonary deposition and kinetics in man and animals (Rundo, ANL; Cohn, BNL; and others).
- 1970–1974 Harvard work on polonium (see chapter 4).
- 1971 Monodisperse aerosols developed in usable quantities at Lovelace and used extensively as exposure modality:
Gates and Warren. Reports on lung pathology from implanted sources (Harvard).
- 1972 Lovelace begins exposures to transuranium elements.
- 1973 et seq. Inhalation work with transplutronics reported from Battelle (Ballou, Sanders, et al.).
- 1974 The “hot particle” controversy is launched (Gofman, Tamplin, and Cochran). Several laboratories begin programs in response, several blue-ribbon committees appointed to investigate. Plan developed that Battelle would use polydisperse aerosols, Lovelace primarily monodisperse aerosols, and Los Alamos to use microspheres.
- 1974 et seq. Los Alamos work on insoluble particles, particularly microspheres, as surrogate for “hot particle.”
- 1974–1975 Reports on “hot particle” problem (spatial distribution of dose) as follows:
WASH-1320, The LMFBR report (Bair, Richmond, and Wachholz)
Biophysical Society
Review by Los Alamos staff (Healy, Richmond, and Anderson)
U.K. report (Dolphin)
NCRP report
NAS–NRC report
- 1975 Long-term studies with rodents at Battelle (Sanders et al.).
- 1975–1978 Harvard work in response to “hot particle” issue (Little et al.).
- 1979 Inhalation work with thorium-cycle nuclides reported from Battelle (Ballou et al.).
- 1980 Interaction of plutonium and cigarette smoke added to Battelle reports on interrelationships (Filipy et al.).
ICRP Publication 31, *Biological Effects of Inhaled Radionuclides* released (Bair et al.).

Chapter 9

Inhalation Toxicology—A Special Entity

Radioactive Dusts and Particles

Overview

The most likely route of intake of radioactive materials in occupational exposure is by inhalation. This is true too, but to a lesser degree, for population exposure. An enormous input of manpower, resources, and ideas was showered upon research concerning the inhalation toxicology of radioisotopes both during and after World War II. As a result, the inhalation work in the atomic energy field became preeminent and led the way for all of inhalation toxicology. It still does.

This rather lengthy chapter reviews the research with dust and particles in contradistinction to materials that are inhaled as gases, the subject of chapter 10. The bulk of exposures are to dusts and particles. The research ties closely to fundamental work with aerosols and thus to general problems of meteorology and air pollution, but these are not stressed except where there is a direct bearing on the biomedical problems or instrumentation therefor. With the ascendancy of lung cancer as a cause of death over the last several decades, and the demonstrated ability of radioactive materials to cause cancer, much of the chapter concerns lung cancer from both qualitative and quantitative points of view.

The chapter begins with a review of the rather considerable wartime efforts with radioactive dust at Berkeley, Chicago, and Rochester. It includes work, particularly at Chicago, that languished in various in-house reports and that has not been generally available in published form.

Turning to the postwar years, the chapter considers briefly continuation of work begun during the Manhattan Project days. There follows a short review of developments in aerosol science and consideration of inhalation work done at the Naval Radiological Defense Laboratory. It then launches into the development of and the work at the large centers for pulmonary radiotoxicology: Pacific Northwest Laboratory (PNL) at Hanford, the Lovelace Foundation—Inhalation Toxicology Research Institute, and the University of Rochester. Following these, we consider the important work done at other laboratories that was not on the grand scale of the major centers but was significant nevertheless: Harvard University; The Health and Safety Laboratory—Environmental Measurements Laboratory of the Atomic Energy Commission (AEC), Energy

Research and Development Administration (ERDA), and Department of Energy (DOE); the Los Alamos Scientific Laboratory; New York University Institute of Industrial (Environmental) Medicine; Oak Ridge National Laboratory; Universities of Pittsburgh and Cincinnati; Wayne State University; and miscellaneous others. There are some short comments on work abroad.

The final section of the chapter considers some special activities that acted as focal points for intensive studies, e.g., the "hot particle" problem, tobacco smoke, and some special U.S. government projects for uses of nuclear materials that might involve inhalation hazards. It concludes with brief comments on the role of the Headquarters offices in nurturing and guiding the entire enterprise.

When we remember that initially the very idea of purposely putting up clouds of radioactive materials in the laboratory filled all concerned with apprehension, it is most satisfying to realize that hundreds of experiments have been done without a serious contamination incident or personnel exposure. The engineering, operational protocols, and smooth functioning of the large groups concerned could only have occurred with major and far-sighted commitment of the federal government. No single industry or institution could have mounted such a program.

The results have confirmed all of the early suspicions regarding the possibilities for developing lung cancer (as well as other cancers) from the inhalation of radioactive dusts and particles. They have allowed a start on quantitation of risk. They have shown that the risk can be controlled. They have demonstrated repeatedly that there can be no substitute for the actual inhalation experiment. And, finally, the convenience of a radioactive tag has contributed much to the understanding of basic respiratory physiology and pharmacology and to basic aerosol science. Nevertheless, the work also demonstrates the great reluctance with which nature gives up her secrets. Many important questions remain unanswered, and the quest must continue, especially in the centers already in place, which are developing new knowledge each day.

1. Introduction

As stated earlier (see overview), the most likely and generally the most hazardous route of intake of toxic materials is by inhalation. This has been, and still is, especially true of occupational exposure. The generalization extends back to the early days of industrial hygiene; in fact to very broad areas.^(a) Special methods are needed for collecting samples and analyzing exposures. Appreciation of the complexity of the problems of evaluation began with the clinical problems of coal miners, of silicosis in hard-rock miners, and workers in

(a) An excerpt from the brochure describing the ten-year old *Journal of Aerosol Science* (Pergamon Press) provides this broad picture: "Aerosol particles suspended in the atmosphere influence life in many ways: airborne infection, treatment of disease, exposure to dust at work, safety of nuclear reactors and α -radiation safety, climatic and local weather effects, air pollution, tobacco smoke, pest control, chemical warfare—almost all the enormous sums of money spent on research and development in the field go in these directions.

Underlying every applied problem in aerosols is a complex of scientific knowledge which has been built up over the last hundred years; little systematic education in aerosol science is available, but the *Journal of Aerosol Science* is concerned with this."

the dusty trades above ground. However, despite progress in evaluating and controlling occupational exposures, a relatively small segment of the effort was devoted to controlled exposures of experimental animals. One reason for this was the problem of producing reliably and repetitively an aerosol of known characteristics. Much early experimental work was done by simply using aliquots of the exposure atmosphere or placing animals in the workplace.

In the 1930s and even into the 1940s, experimental work in the United States involving inhalation exposures (in contrast to the fundamental behavior of particles) took place in physiology and pharmacology laboratories interested in asphyxiants and some of the more violently toxic gases; in a few enlightened industrial medical departments around the problems of volatile organic solvents; and, for exposure to particles, in laboratories like the Bureau of Mines, the U.S. Public Health Service Division of Industrial Hygiene, and special university laboratories such as the Kettering Laboratory in Cincinnati. Even a perfunctory review of these enterprises is impossible here, except to recommend that the reader consult the general industrial hygiene literature of the day, and find the series of monographs from the U.S. Public Health Service on silicosis and later from the National Institute^(a) of Health under the editorship of L. Fairhall on the toxicology of a large number of inorganic substances, and the miscellaneous publications from the Bureau of Mines.

The primary reason for the relative paucity of experimental work (as compared to clinical evaluations) was the complexity of aerosol science^(b) and the difficulty of doing experimentally what theory indicated needed to be done. However, under the combined impetus of advances in meteorological science, the urgent problems of the chemical warfare services (at Porton in the United Kingdom and at Edgewood Arsenal in the United States), and particularly the development of the electron microscope, aerosol science leaped forward dramatically in the late 1930s and early 1940s. Here, too, space interdicts any detailed formal discussion, except in connection with the specific problems surrounding radioactivity, which we shall take up in due course. Let it be said, however, that the developments were very much a two-way street. Just as the progress of general aerosol science made possible the study of radioactive aerosols, so did the convenience of measuring small amounts of radioactivity contribute to the understanding of aerosol behavior.

We have termed inhalation toxicology "a special entity" and chosen to discuss it separately, even though the eventual toxic effect of a material once absorbed from the lung may be similar to that of the same substance introduced by other routes. This is partly because of the unique methodologies involved and the development of specialists in the field, partly because of the special problems involved in effects on the lung. For convenience, in this chapter we will consider the most common types of exposure modalities: dusts, mists, smokes, and other situations where particulate material, either liquid or solid, is suspended in air; situations where the exposure modality is a gas, or behaves like a gas, will be deferred to chapter 10.

(a) It was one institute in those days. The experimental work was done in the Division of Industrial Hygiene; field and industry-oriented work was under the Bureau of State Services.

(b) General definitions can be found in the industrial hygiene literature and will not be repeated here. "Aerosol" refers to any suspension of material, solid or liquid, in air, just as "hydrosol" refers to a suspension in water. Stable aerosols are always of relatively small particle size.

II. The Manhattan Project Days^(a)

A. The Earliest Concerns

It did not take long for those concerned with potential health hazards from the radioactive materials about to be handled or produced in the Manhattan Project operations to realize that the inhalation route might be of even greater significance with radioactive materials than in more conventional situations. One of the earliest reports, done in 1942, contained a calculation by Failla on "Tolerance Concentration of Radioactive Gases in Air" (Failla 1942). This bore primarily on energy absorption in various portions of the lung. Each laboratory developed, for its operations, methods and standards for evaluating airborne radioactivity, as seen in the monthly and special reports of the Manhattan Engineer District (MED), copies of which the author obtained from several sources. Examples are the report prepared by Koval (1945) at the Clinton Laboratories and the detailed review of Clinton Laboratory procedures for air monitoring by Parker (1946). Similar documents can be found for Hanford operations.

Very early there was much concern for the hazard from radioxenon contained in the off-gases from the early "piles." The first experimental animal inhalation exposures under MED auspices were around the problem of radioxenon. This was set up at "Site X" (Clinton Laboratories) after calculations of the probable amount of activity to be expected and preliminary experiments.

One of the earlier monthly reports from the Metallurgical Laboratory tells that Waldo Cohn, who is now identified primarily with Oak Ridge,^(b) visited Dr. Hamilton's laboratory at Berkeley to assist in a model experiment on gaseous fission products. The same report describes similar preliminary experiments on radioactive gases produced in the Chicago cyclotron. This was carried out by E. R. Tomkins, whose later work went in quite different directions.

The major internal emitter toxicology programs were at the two Metallurgical Laboratory "branches," Berkeley and Chicago, which we reviewed in chapters 6 and 7. They added inhalation experiments where and when feasible. A surprising amount of information was developed despite the rather crude techniques. Beginning slightly later, (work begun in 1943 and reports appeared soon thereafter), the University of Rochester Project undertook major efforts in inhalation toxicology and gradually became identified as a major center for this type of work. We saw some of it in the chapter on uranium (chapter 2) but must add more details in this chapter.

B. Inhalation Work at Berkeley Under the Manhattan Project

The work at Berkeley appears to have been done in two distinct phases. The first concerned inhalation of gaseous mixed fission products. The second utilized either individual radioisotopes in the later times when carrier-free materials were available as described in chapter 6, or aged mixed fission products with or without the parent uranium or plutonium. In addition, the behavior of plutonium in various forms was examined.

(a) Officially the period of work under the Manhattan District Corps of Engineers.

(b) Dr. Cohn was among the first to formalize internal dose calculations, including inhalation. See reproduction of one of his early postwar declassified papers (1948) in the silver anniversary volume of *Health Physics* (Cohn 1980).

The work on mixed fission products paralleled, to a degree, the broad program at Berkeley on the behavior of unseparated fission products given to animals orally and by intraperitoneal and intramuscular injections. However, the apparatus needed was much more complex in order to catch the products in their initial gaseous state.

To get a start, uranium metal was subjected to deuteron bombardment at the Berkeley cyclotron, and the aerosolized products were inhaled by rats. This was before the pile was in operation. (See "Emanation Experiments" in Hamilton's monthly report for February 1944.) A picture of the apparatus used for this exposure is shown as figure 9.1.

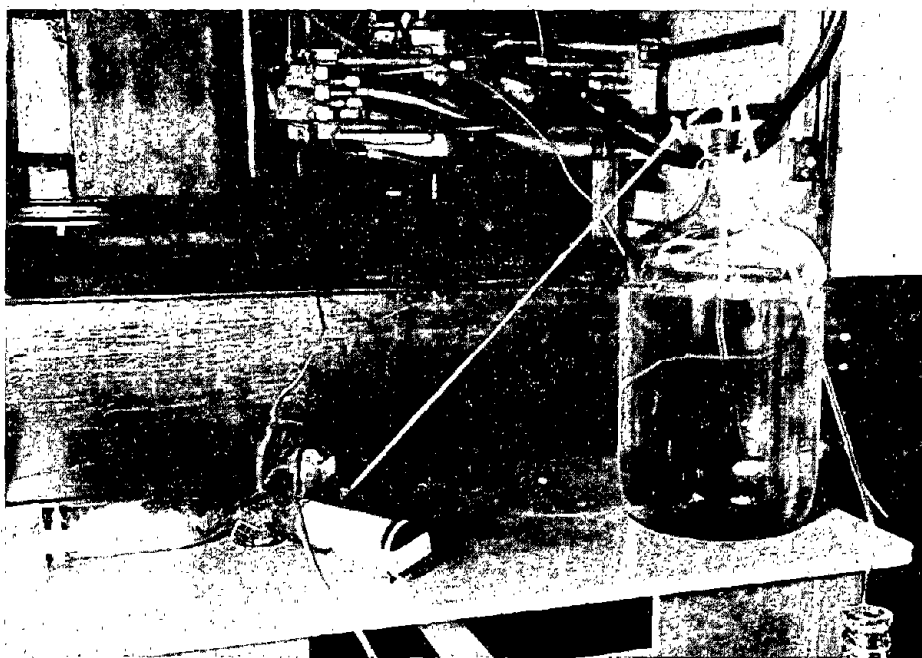


FIGURE 9.1. Equipment for "Emanation Experiment" at Berkeley. The equipment for preparing the aerosol is essentially within the cyclotron (background) and separate from the animal exposure unit. (Photo courtesy of Dr. Patricia Durbin; report by Hamilton 1944, and Hamilton and Scott 1944.)

Later, some of the work was done right at the "pile" (reactor) at the Clinton Laboratories after it came into operation. Here the radionuclides at the very head end of the fission product chain were primarily involved. Since many of these are normally gaseous, they could be brought into the exposure system as gases, but would very promptly decay to their short-lived, normally solid degradation products. Since elimination from the body was rapid, only a small part of these exposures involved the longer-lived fission products. However, the work gave an opportunity to develop ideas about the pulmonary behavior of the most abundant of the fission products.

A schematic of the apparatus used in the pile, modified slightly from the one major report prepared on this early inhalation work, is shown as figure 9.2 (Scott

et al. 1945). In addition to the products of neutron bombardment of the foils, the mixture included also the normal radioactive gases, such as radioxenon, circulating in the pile.

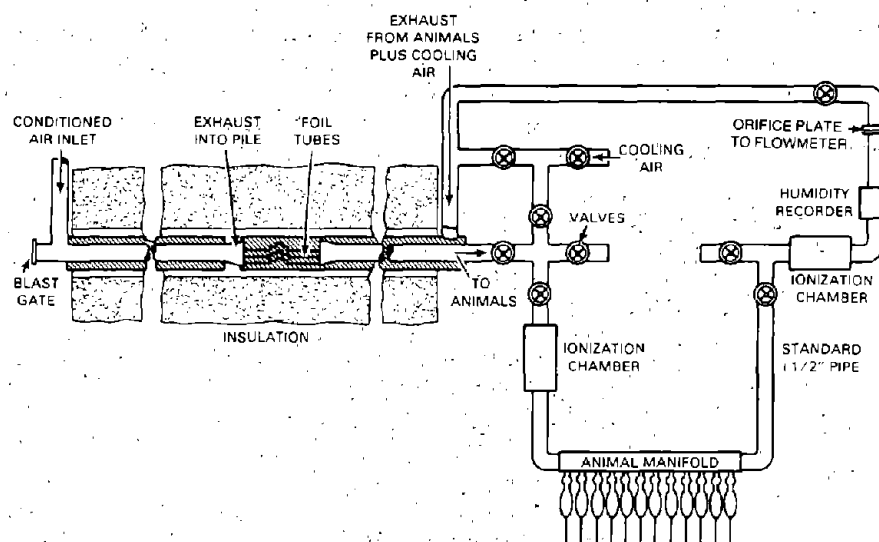


FIGURE 9.2. Schematic diagram of apparatus for in-pile production of short-lived fission products and animal exposure manifold. (Redrawn from Scott et al. 1945.)

Both pieces of work suggested that the principal descendants from the emanation mixture inhaled by the animals were strontium and barium, plus rare earths and zirconium, which were found in soft tissues.

With the in-pile system, the composition of the mixture could be varied somewhat by manipulating the hold-up time in the reactor. Elimination time from the upper respiratory tract was very rapid. (Nine-tenths of the original activity was either absorbed or eliminated by sixteen days.) Small differences in clearance occurred with different hold-up times. The deeper lung sometimes cleared less rapidly. Most of the soft tissues held only small amounts of activity, and this was lost rapidly. Thyroid accumulated very large activities initially, presumably from absorption of radioiodine, but it left rapidly enough so that after a few days thyroid was usually comparable to other soft tissues. Only skeleton retained significant amounts over the longer periods. Feces were the predominant route of excretion, with urine significant only at early times. This latter may represent excretion of the more soluble entities present in the initial mixture.

Most of the subsequent inhalation studies were done at Berkeley rather than at the pile (at least the reports do not indicate to the contrary) and involved either an aerosol spray, burning of thin metal foils, aerosol production in an electric arc between graphite rods, or sparking in a high voltage discharge.

This work was published in condensed form in 1949 (Scott et al. 1949) by most of the authors of the earlier progress report (Scott et al. 1945). This seems to be the only formal report from this fairly extensive amount of work. The authors regarded both the techniques and scope of the work as preliminary and placed

less emphasis on it than on the mainstream work utilizing other routes. Nevertheless, the outlines of much of the future of inhalation toxicology can be discerned in the results, and they deserve more than passing mention.

Most of this later work used either fissionable material like uranium or plutonium, fission products that had aged for appreciable periods, or a mixture of the fissionable material and fission products or separated elements. For the fission mixtures there either had to be, or the investigators chose that there be, appreciable periods of aging between removal from the reactor and the actual inhalation experiment. Thus, this work differs from the earlier work at the cyclotron and the pile by involving primarily the longer-lived fission products and some of the important alpha-particle emitters.

The specific aerosols and a glimpse of the production techniques are given in the following excerpt from the cited publication.

The specific aerosols used in these studies were prepared as follows:

1. Plutonium nitrate as $\text{PuO}_2(\text{NO}_3)_2$ is soluble in ethyl ether. Advantage was taken of this property by introducing the plutonium nitrate into the exposure chamber as a spray. Very small particles free from ether were produced by forcing the ether-plutonium solution through a gold jet after it had been allowed to come into equilibrium with carbon dioxide at a pressure of 760 pounds per square inch (53 Kg. per square centimeter). An effervescent ether-plutonium solution was produced when the jet was directed into the warm exposure chamber, the temperature causing the ether to evaporate. The plutonium yielded to the rat was about 10 per cent of the total plutonium per exposure. The exposure time was 3 to 4 minutes. . . .
2. Aerosols of plutonium in the plus four state as plutonium oxide (PuO_2) were produced by burning the plutonium salts and the plutonium metal itself. In the former instance, the solution was evaporated on graphite electrodes, and in the latter the metal was embedded in holes drilled in the centers of the 1/16 inch graphite rods. In both cases the electrodes plus the plutonium were burned in an atmosphere of oxygen in an electric arc. Two hundred micrograms of plutonium were burned for each exposure. The amounts yielded to the rats varied from 4 to 7 per cent of the material burned. . . .
3. Aerosols of fission products occluded in uranium as uranium oxide (U_3O_8) and plutonium as plutonium oxide (PuO_2) were produced in a similar manner. At the time of exposure the radiations from the fission products predominated. The ratio of fission product disintegrations to the alpha particles arising from the uranium was about 20,000 to 1. The age of the fission products was 2 to 3 months. About 80 mg. of uranium metal was burned at each exposure of 30 seconds' duration. The yield to the rats was about 1 per cent.
4. Carrier-free fission products were also prepared as an aerosol by evaporating the uranium-free solution on graphite rods and burning these. The solution of fission products used was 6 months to 1 year old. Owing to this fact, the fission products with short half-lives had decayed away. The fission elements remaining then were composed primarily of Sr^{89} and Sr^{90} , Y^{91} , Zr^{95} , Nb^{95} , Ru^{106} and Ru^{103} , Cs^{135} , Ce^{144} , and element 61¹⁴⁷.
5. Zr^{89} was used in a study of a human subject (one of us). The short half-life of this material, as well as the absence of long-lived radioisotopes, precluded any danger of excessive amounts of radiation to the subject. The active material was suspended as an aerosol in argon as follows: The Zr^{89} solution was evaporated on two concave gold buttons 1 cm. in diameter. It was then dispersed in argon by passing 15,000 volts between two electrodes which were placed 5 mm. apart. A 0.01 microfarad condenser was connected across the high voltage line. Oxygen was avoided in the chamber because of the production of undesirable amounts of ozone. Approximately 1 microcurie of Zr^{89} was inhaled by placing in

the left nostril a short rubber tube which was also connected to the generator. The inhaled Zr^{89} was exhaled through the mouth into a glass wool filter, followed by several breaths of inactive air, so that the percentage of material exhaled could be calculated.

6. Carrier-free protoactinium, which has a 30 day half-life, was prepared as an aerosol by sparking evaporated Pa^{233} solution on a gold electrode in a high voltage electric discharge. This was administered to rats in the same manner as Zr^{89} .

Except in the Zr^{89} and protoactinium studies, the size of the particles produced by the aerosol generators was determined by collecting representative samples on amyl acetate films. The particle size was estimated with the aid of an electron microscope.

(Scott et al. 1949, pp. 4,6)

The exposure chambers were each on the same plan, i.e., made of metal with an annular arrangement of holes to accept the nosepiece from the animal. They are diagrammed in the publication cited and will therefore not be reproduced here.^(a) The section of the chamber for the arc or spark "explosion" seems perilously close to the animal array, but the authors make no mention of problems except that the arc was produced in a pure oxygen atmosphere to avoid production of dangerous amounts of carbon monoxide. Heroic measures were taken to guard against entrance through the mouth by sealing and sewing the lips together under anesthesia.

Particle sizes were measured, but the results given are as an average with range rather than by the conventions now used, so that the size distribution can only be guessed at. On the whole, the smokes had typically submicronic average diameters, but the range was sometimes quite large (e.g. 0.06 to 38 μ for PuO_2 [NO_3]₂ in the electric arc). The "spray" produced by evaporation of an ether solution was reported as having an average particle size of 0.25 μ with a range from 0.01 to 0.6 μ . None of this work involved quantities likely to assume the characteristics of "dusts," i.e., larger average particle size.

Rather extensive autoradiographic work was done on both the aerosols and the tissues.

The results can be generalized as follows:

1. Many substances that were readily absorbed into the body and went, for example, to bone after parenteral administration were not readily absorbed from the lung. Instead, they formed insoluble complexes which were usually cleared out rapidly by the ciliary clearance mechanism. Sometimes a portion remained in the deeper lung for appreciable periods.
2. The major depositions were in the upper respiratory tract and were moved out promptly by the normal clearance processes.
3. The investigators were evidently surprised at the mobility of some materials from the alveolar regions.
4. Except for a hint that particle size might influence subsequent behavior, as well as deposition, the materials once through the lung barrier seemed to distribute to the tissues much as after other routes of administration.
5. Nevertheless, the behavior of inhaled materials could not be predicted. Thus, there could be no substitute for information obtained by inhalation experiments.

(a) Units of similar plan were designed at Chicago, and since these have not been published, they will be pictured, and a comparison will be made in the next section.

6. The difference in lung absorption between plutonium nitrate spray and the plutonium oxide aerosol underscored dramatically that even a given element might behave quite differently in different chemical forms.
7. Lung clearance can soon lag behind that from the upper respiratory tract. In fact, there is essentially no long-time residence of these materials in the upper tract.
8. The experiments were all at tracer rather than effects levels, and none went beyond sixty-four days after administration.
9. Larger average particle sizes resulted in greater deposition in the head, less in the deeper respiratory tract.
10. Ruthenium and cesium were very rapidly eliminated and were not retained in the skeleton.
11. Using plutonium oxide, it was determined that about 75% of the material entering in a single inhalation remained in the body. The particles exhaled were 0.5 to 1.0 μ in diameter. (A special valve system was constructed for this experiment.)
12. In the single human inhalation study, using zirconium, almost all of the inhaled activity was retained. Rats retained a lesser fraction (about 70%).
13. Lung clearance via the ciliated epithelium seemed to occur at about the same rate for all substances tried. All the materials fell within a relatively narrow band on a graph of elimination as a function of time.
14. In these experiments there was little evidence that the materials entered the lymphatic system.

To conclude this brief discussion of the Berkeley work, we refer to studies using the intratracheal method of placing materials in the lung. Such work is described by Hamilton in a monthly report issued in February 1945 (Hamilton 1945). The autoradiography indicated very uniform distribution of ruthenium in alveolar sacs and ducts, while distribution of zirconium and columbium was completely random. Yttrium, cerium, fission mixture, praseodymium, and neptunium showed intermediate behavior. There was no material in the trachea or bronchial tree. On the whole, the tissue distribution was similar to that after parenteral administration. This latter indicates that the intratracheal insertion of a solution into the lung is not a suitable surrogate for the more cumbersome and difficult inhalation experiments. Scott et al. indicate an awareness of this point, but it is not emphasized.

A graph showing the percent retention of eight elements as a function of time up to sixty-four days is reproduced from the Hamilton report as figure 9.3. Note that there are real differences in both initial deposition and in clearance after the intratracheal administration of these substances. A similar graph made from the inhalation experiments would show faster clearance because much of the material is deposited in nasopharynx and bronchi, from which clearance is uniformly rapid. Also, the differences among elements would be less noticeable. The primary difference might be the greater mobility of the fission products of plutonium, compared to plutonium itself, even when introduced together as a single aerosol.

Nothing is said in the descriptions of the Berkeley work of any measures taken to guard against the health hazards to the operators of purposely producing a radioactive aerosol, even if in a closed system. Presumably these matters are buried away somewhere in the records of the health physics or health and safety operations of the day. In light of the elaborate precautions taken in the

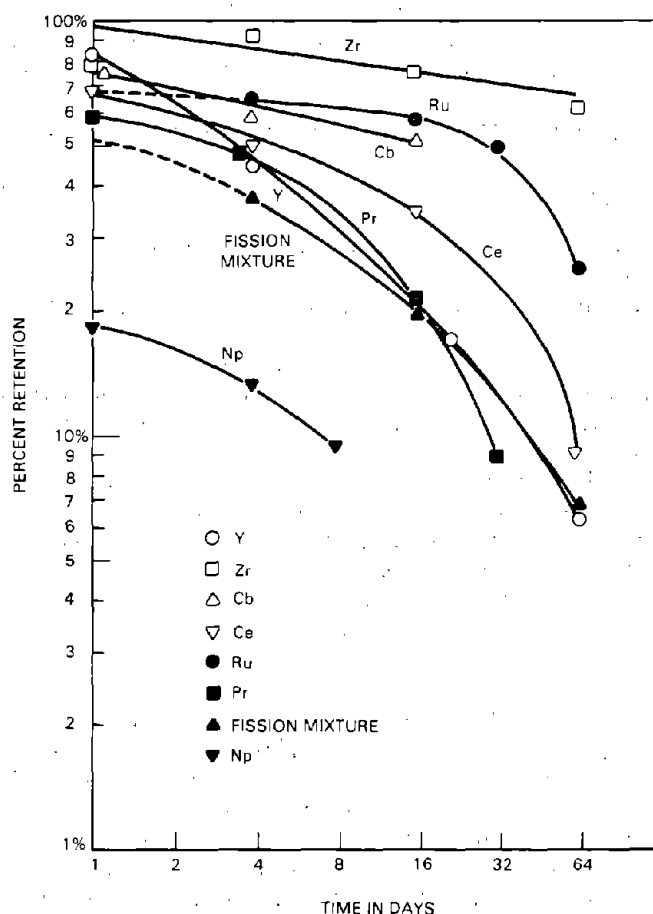


FIGURE 9.3. Percent of total retained activity deposited in the lungs following the intrapulmonary instillation of carrier-free fission products. (Redrawn from Hamilton 1945.)

postwar development of radioactive inhalation programs, this hiatus must reflect, in part, the characteristic drive in the Manhattan Project to get the information as rapidly as possible, in order to provide guidance to those planning and operating the production facilities. Yet, it is certain that personnel protection was considered.

C. Inhalation Work at Chicago Under the Manhattan Project

1. Commentary

There was much more inhalation work done at the Metallurgical Laboratory installation in Chicago than is generally realized. The bulk of the work is contained in monthly reports and in detailed specialized reports in the "CH" series. Essentially none of the work was published in the open literature. Several

reports were indicated as destined for the "Plutonium Project Record," which later became part of the National Nuclear Energy Series (NNES). Nine reports on inhalation work with "CH" and "MDDC" numbers were slated for publication in volumes 22G and 22H of the NNES. These were among the three volumes in the Chicago series that never reached publication. (See "NNES Hiatus" in Appendix C). For this reason, and because of the extensive and detailed studies involved, the work will be reported here in more depth than might otherwise be necessary, as was done in earlier chapters concerning other unpublished Chicago work (cf. chapters 1, 6, and 7).

The early Chicago work had a common denominator with Berkeley around the potential problems of the radioactive off-gases from reactors. It is difficult to assess the degree of collaboration that took place. The problems of radioxenon kicked off the Chicago reports, just as they did those from Berkeley. And there clearly was collaboration around concerns for the potential exposures at the Clinton Pile. However, the bulk of the work and reports from Chicago give every indication that most of the developments were fairly isolated from Berkeley, and vice versa. With tight security in effect, it is likely that only those in the highest echelons knew the broad picture. Even if there was knowledge at the working level, it would be unlikely to appear in written reports.^(a) Whatever the reason, there is much duplication in the inhalation work of the two laboratories. However, it was more extensive, more methodical, and appeared to occupy a more central position in the program at Chicago, features that have not been obvious heretofore.

In preparing this section, this author has had a plethora of resources. The story was seen in its very early stages by the acquisition some years ago of a complete set of monthly summaries of "Group Experiments" from May 1944 through November 1945, prepared by Dr. R. Abrams.^(b) This set includes hand-drawn graphs and occasional calculations. It was supplemented by copies of the Met Lab declassified monthly reports from May 1943 on, many short reports on special subjects obtained from several sources (Berkeley, Oak Ridge, Argonne, Battelle, and the files of Dr. Hymer Friedell), and the selected review items in the chapter on Chicago work in Friedell's book (Friedell, in press).^(c) Finally came the summary reports written for the "CH" and "MDDC" series.

This report provided an especially good opportunity to see the evolution from what seemed at times to be halting, somewhat repetitive, and haphazard probings into various aspects of the problems, to a final product that is highly organized and crisply pertinent.^(d) This difference between the day-by-day events and the much later refined reports and publications is remarked upon also by Friedell.

(a) An exception is some remarks in a Chicago report on the methods used by Hamilton for the inhalation of short-lived fission products at the reactor.

(b) The typewritten portions are identical with the declassified monthly reports seen in Dr. Friedell's files, but the notes have, in addition, the personal touch.

(c) Manuscript for book seen in draft form. This author is most grateful to Dr. Friedell for sending a prepublication copy of this volume, as well as for an opportunity to peruse his report files and make excerpts from them.

(d) Obviously, this phenomenon is not unique to the wartime research efforts. It applies, to some degree, as we all know, to the evolution of all research into new territories. However, the presence of security restrictions amplified the phenomenon for the Manhattan Project work.

2. Aerosol Production Methodologies at Chicago

Abrams and his coworkers labored so consistently at the problems of producing aerosols of radioactive materials that more is said in the Chicago reports on this subject than in those from any of the other inhalation programs.^(a) For this reason, we should take time to review what they did and what they found.

Almost every monthly report contained a paragraph or so on the attempts to prepare reproducibly an aerosol that would reach the experimental animals in sufficient quantity and of the correct particle-size range to produce measurable depositions in the respiratory tract. It was a dreary recital of discouragements. The amounts of radioactive materials were minuscule at the start of the program. Method after method deposited the bulk of the aerosolized elements on the chamber walls, or left it behind in the generator. Thus, most of the early trials utilized techniques intended to produce vapors, e.g., carbon arcs, high voltage sparks, high-energy condenser discharges, burning of thin wires coated with the material or made of the material, etc. Aerosols of soluble substances were produced by a variety of liquid atomizers.

In contrast to the Berkeley group, the Chicago workers hoped to aerosolize enough material to produce biological effects, as well as to measure tissue distribution and excretion. This made the low efficiency of the methods especially discouraging. Yet, the effort when summarized in an MDDC report in 1946 is impressive (Abrams et al. 1946a). The basic outline of this report covered the following topics:

- Production of Aerial Dispersions
 - Dry Dusting
 - (a) Waring Blender
 - (b) Elutriator
 - (c) Elutrimizer
 - (d) Insufflator
 - Atomization of Aqueous Solutions
 - Atomization of Non-aqueous Solutions
 - Incinerator
 - Production of Aerosols in a Carbon Arc
 - Production of Aerosols in a High Voltage Spark
 - Production of Aerosols in a High Energy Condenser Discharge
 - Production of Aerosols in a Chemical Explosion
- Quantitative Estimation of Air-borne Radioactive Material
 - Measurement of Air-borne Particles—The Ultramicroscope
 - Methods of Collecting Particulate Matter from Air
 - (a) Filter Paper
 - (b) Electric Precipitator
 - (c) Thermal Precipitator
 - Analysis of Collected Samples
 - (a) Estimation of Concentration
 - (b) Estimation of Particle Size

An idea of what the authors thought most worthy of comment can be obtained from the abstract of the cited report, which is quoted below:

(a) The Rochester program, which dealt with aerosol problems in depth, was working primarily with uranium dust, a very weakly radioactive substance.

The biological program calling for exposure of animals to air-borne radioactive materials made it necessary to develop procedures for producing aerosols, exposing animals to the aerosols, and measuring particle size and concentration. Since carrier-free materials were used, techniques were devised for the remote control handling of material with negligible weights, but with high radioactivity so as to obtain maximum deposition in the lungs of the experimental animals.

Of a number of methods of producing aerosols that were investigated, three were extensively used. Atomization of aqueous solutions in a right angle jet atomizer was useful for tracer. But because of the great dilution with air it was not possible to obtain high efficiency. Burning a salt in a D. C. carbon arc was adequate for obtaining high intensity fission product smokes, but failed with Pu where it was necessary to use larger masses of material. High concentration Pu smokes were obtained by wrapping Pu metal in thin aluminum foil and discharging a high energy condenser (1000 joules) through the foil.

To maximize lung deposition and to avoid skin contamination and ingestion we use anesthetized rats which breathed from a small chamber through glass cannulae. This chamber consisted of a 2.8 liter brass cylinder from which 32 rats breathed while lying on a surrounding bakelite superstructure. In the case of the exploding foil it was necessary to use a 4.1 liter cylinder with a partition which protected the rats from the violence of the explosion.

A number of methods were investigated for collecting smoke samples for analysis. The most satisfactory was the thermal precipitator which makes use of the dust-free zone around hot bodies to precipitate all the particles in a sample of air on to a Parlodion-coated microscope cover slip. Concentrations were estimated by doing direct α and β counts on these cover slips. Later the Parlodion film was stripped off the glass and mounted for particle size observation in the electron microscope. Mean particle size with the methods used in our experiments averaged 0.1 to 0.2 μ . (Abrams et al. 1946a)

The details of these methodologies are largely of historical interest. We now have better methods. Yet, a few notes on what happened are pertinent.

The methods for handling dry dusts, e.g., elutriator, elutrimizer (a combination elutriator and atomizer), and the conventional insufflator required too much material to be useful for any but low-specific-activity materials such as uranium oxide. Only a small amount of work was done at Chicago on inhalation of uranium compounds.

The carbon arc finally worked well for fission products and uranium, but never could produce high concentration plutonium smokes. The electrodes had to be of as pure carbon as possible since a large proportion of the aerosol was made up of volatilized alkaline earths and carbon particles from the electrodes. Fortunately, the autoradiographic method made it possible to work out sizes of the radioactive components. The size of the chamber was critical. If it was too small, the animals were too near the arc. If it was too large, most of the material was lost to the chamber walls. A diagram of the carbon arc system used most is shown as figure 9.4.

Plutonium smokes were not satisfactory from the high voltage spark. They were prepared at useful concentrations with high-energy (37,500-volt) condenser discharges. Unfortunately, the explosion produced by this sudden release of energy required a chamber divided into two sections. The aerosol was produced in an upper section and diffused to the animal array connectors by opening a door to the lower section. This reduced efficiency and thus the yield.

The atomization of water-soluble solutions produced satisfactory aerosols only after much experimenting with details of the atomizers, such as the angle of entrance of the jet from the solution reservoir. One of the best of these was

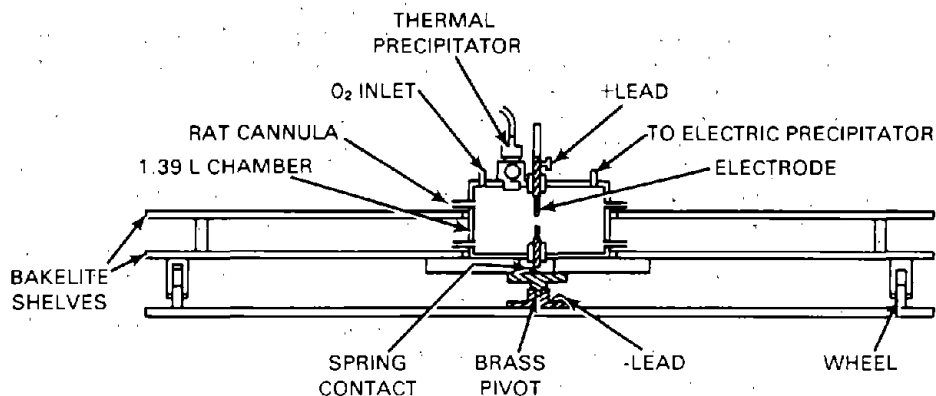


FIGURE 9.4. Diagram of cylindrical "merry-go-round" chamber for the exposure of rats to arc aerosols. The chamber was a brass cylinder 6 in. in diameter and 6 in. high, and was seated in a slight depression in the center of a circular Bakelite shelf 26 in. in diameter. A second such Bakelite shelf was mounted 2 in. above the lower one and was removable so that one had free access to the lower shelf. The entire unit of shelves and chamber rotated on a brass pivot, being balanced by small brass wheels under the lower shelf. About 1/2 in. above each shelf 16 uniformly spaced holes through the chamber were filled with 1/8 in. rubber grommets. On each shelf 16 anesthetized rats were laid supine, and tracheal cannulae projecting from their mouths were pushed into the chamber through the grommets. The bottom of the chamber was covered with a layer of CaCl_2 , soda lime, and Hopkalite to control humidity, CO_2 , and CO . Carbon electrodes were mounted through Bakelite insulators along the axis of the chamber. (Redrawn from Abrams et al. 1946a, pp. 33-34.)

one designated as Type II. This is diagrammed in figure 9.5A. However, these were made of glass and were hard to duplicate and to clean. To avoid having to decontaminate the jet and use it over, Abrams and colleagues turned to a simple metal jet that could be discarded. A diagram of this is shown as figure 9.5B. Either unit could be attached to an exposure system such as that shown in figure 9.5C. Since plutonium is soluble in some organic liquids, attempts were made to derive aerosols of plutonium from them. Freon did not work well, but the "ether bomb," in which plutonium is dissolved in dimethyl, or diethyl ether, was moderately satisfactory. For reasons that are not clear, the method did not seem to work as well as the similar one used by Hamilton and colleagues at Berkeley. However, the efficiency requirements the Chicago people placed upon themselves were more demanding than for the work at Berkeley done at tracer levels only.

Particle sizes were usually reported in terms of the average with range. However, with some aerosols, e.g., ^{144}Cs from a carbon arc, the size frequency distribution and a probit plot were given in the manner being adopted by the aerosol scientists working in other fields.

It can be seen that the production of aerosols of radioactive materials presents some unique and difficult problems. Most of them were associated with the very small mass of material to be used, brought about early by the scarcity

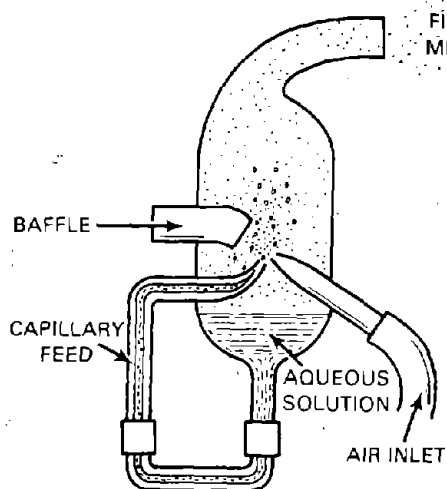


FIGURE 9.5A. Right angle jet atomizer, Type II. It was necessary that the stream of dry air be introduced coaxially with the atomizer stream to prevent a cyclone effect from plating all the particles out on the wall. The strong Tyndall effect faded almost completely within a centimeter beyond the mixing point, thus indicating great diminution in surface area, i.e., evaporation. It was usually desirable to have the flow rates of saturated and dry air approximately equal. In most experiments with the Type II atomizer, the air stream containing the radioactive aerosol passed through a manifold to which were attached 21 rats by cannulae inserted loosely into the precipitator. A pump pulled about 20 l/min through the precipitator and through an asbestos filter paper beyond the precipitator. The complete setup is shown schematically in figure 9.5C. (Redrawn from Abrams et al. 1946a.)

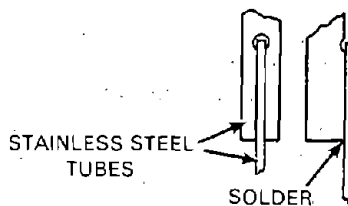
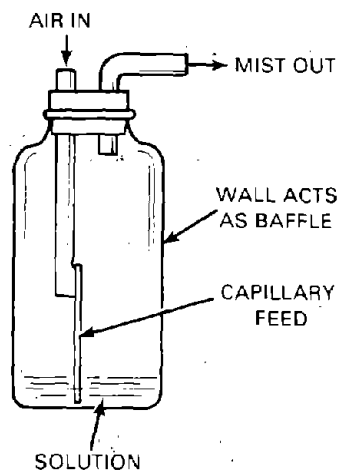


FIGURE 9.5B. Right angle jet atomizer, Type III. The capillary feed and conducting tubes were made of metal. (Redrawn from Abrams et al. 1946a.)

of these new radioisotopes, later by the high radioactivity associated with even very small masses of some materials. Even so, it was not uncommon to have millicurie amounts of activity used for single exposure attempts, only to have most of it go to the chamber walls.

As at Berkeley, relatively little is said in the Chicago reports about health protection and contamination prevention measures. There is description of a

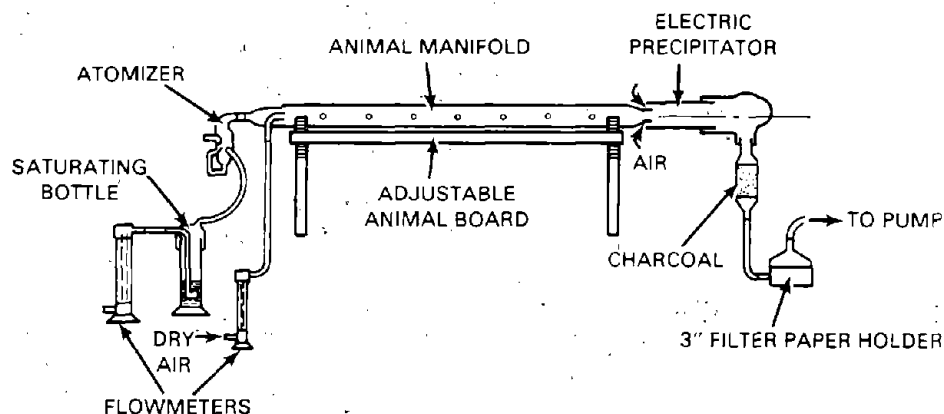


FIGURE 9.5C. Manifold technique for exposing rats to aerosols. The mist from the atomizer is mixed with dry air to be passed down the glass manifold into which the animals' snouts protruded. Either the Type II or Type III atomizer could be used. (Redrawn from Abrams et al. 1946a.)

special shield to use for loading hard beta emitters into the carbon arc. Also, it is stated that the exposure apparatus at the piles was probably arranged also for the laboratory work at Chicago. However, the reports are relatively silent on these aspects.

3. Metabolism of Short-Lived Airborne Fission Products

A cooperative effort was carried out at Oak Ridge (Clinton Laboratories) in 1944. It involved in-pile irradiation of uranium foil with gas passing over it to pick up the fission recoil atoms and to carry them to animal exposure chambers and recording equipment outside the shield. The work was written up in May 1945 by Lanz and Teresi (1945) as a CH and later an MDDC report slated for publication in Vol. 22H of the NNE series.

The interrelationships between the work reported from Chicago on short-lived airborne fission products from the pile and the somewhat similar work reported from Berkeley are not well documented. The report of Lanz and Teresi has inscribed on it, "This work was performed at Oak Ridge, Tenn. (Clinton Labs) in 1944."

The puzzling fact is that the 1945 summary by Scott et al. reports Berkeley work with short-lived fission products from the Clinton Pile^(a) with exposures stated to have been conducted between November 7 and December 10, 1944, apparently after the Chicago work.^(b) The apparatus used is the one pictured in figure 9.1. The Chicago apparatus, pictured in Lanz and Teresi, is quite similar. However, the report from Berkeley makes no mention of any preceding work done by people from Chicago or anywhere else. We must conclude that the two laboratories conducted quite similar work at the Clinton Pile, but we can only conjecture whether they were entirely independent or only appear so

(a) This was reviewed in section II B.

(b) Both reports were originally in the classified CH series and later declassified in the MDDC series.

because of the security requirements of the day, which might have governed what was said in a report.^(a) Fortunately, the results, to the extent that they overlap, are not in conflict.

Construction and calibration of measuring and recording equipment are documented in some detail by Lanz and Teresi. Composition of the "hot gas" was found to include 77-hr tellurium, 12.5-day barium, several strontium isotopes, and three radioiodines. The presence of radiotellurium was taken as evidence that solid primary fission products reached the animals.

The biological results soon demonstrated that the external radiation dose to mice exposed to the fission recoil gases accounted for all effects in the lethal dose range. This was concluded from an experiment in a small chamber with the animals immersed in the gas. In addition, rats exposed and set aside for periods of up to a year showed no discernible difference from controls beyond the period of acute effects. This was taken as evidence that the deposited radionuclides did not produce significant effects.

The manifold device described above was constructed to eliminate the external radiation dose except to the nose and mouth of the animal. This would thus allow effects of internally deposited radionuclides to predominate if they could. The only effect seen, in acute experiments, was radiation burns of the mouth and upper respiratory tract. Some of these animals lost weight and died—apparently from starvation brought on by inability to eat. Those animals that lived beyond this period recovered completely for the duration of the experiment, which appears to be about forty-five days. The starvation hypothesis was tested further by giving a normal caloric diet to some of the rats intraperitoneally. Survival was increased sufficiently to suggest that the hypothesis was approximately correct.

Results of gross and microscopic pathologic examination indicated nothing beyond the mouth and nose region. It was concluded, on these bases also, that internally deposited radioactivity played no role. In these days of appreciation of the latent periods required for development of radiation effects, particularly from deposited radionuclides, the observation periods for pathology in these experiments seem ridiculously short. However, the metabolism work, to be reviewed presently, indicates relatively little retention, even in bone, so that an experiment for long-term effects would probably have been negative. The authors' conclusion that the hazard from short-lived fission products is much greater from external radiation than from internally deposited radioactivity is probably correct.

The metabolism work extended to about sixty days after exposure. While loss from the body was quite rapid, there appeared to be a larger proportion retained than in the Berkeley work. This may reflect the different composition of the mixture. About 25% of inhaled material went to skeleton from lung and was excreted very slowly (half-time about two months); of the amount in lung, about 8% was lost slowly; about 6% was excreted slowly from liver. The balance, in each case, left the body relatively quickly. The highest specific activity occurred in the thyroid. Absorption from the gut was much smaller than from the lungs.

Typical excretion curves showed an initially rapid loss via urine followed by approximately equal loss rates in feces and urine. *This contrasts not only with*

(a) The work using cyclotron bombardments at both Berkeley and Chicago mentioned in the previous section, of course, antedated the in-pile irradiations.

the Berkeley work, but with most other work on inhaled fission products. The reason is not clear.

Autoradiographic studies of the lungs showed uniform distribution of these materials over bronchial and alveolar surfaces. This is consonant with the Berkeley work, and both are in contrast to the behavior of plutonium and many mixtures of long-lived fission products. It probably indicates the predominance of gaseous materials in the initial inhaled mixture.

Attempts to increase the hold-up time sufficiently to get a higher percentage of long-lived fission products failed for technical reasons. It was necessary to turn to quite different experimental approaches to accomplish this, as we shall see presently.

4. Work at Chicago with Longer-Lived Fission Products

Monthly reports beginning in April 1944 carried brief reports of work in progress on inhalation of individual longer-lived fission products. The first moderately detailed report concerned carrier-free 330-day ruthenium and radiocerium administered as aerosols. The ruthenium experiment demonstrated the phenomenon of early rapid clearance from the lung. Over 50% was lost in the first day, followed by a much slower rate of loss with a half-time of over thirty days. Further experiments showed that the ruthenium might be changed in valence state in the lung. Ruthenium chloride in +3, +4 valence state was cleared less than half as fast as ruthenium vapor in the valence 8 state (Met Lab Report 1945a, pp. 15-16).

When cerium experiments progressed beyond sixty-eight days of holding time, the beginnings of hypertrophy of lung cells were noted, but no metaplasia. Lung inflammation was spreading and becoming more intense (CH-2904).

In the next month, Wender and Dailey (Met Lab Report, 1945b) added the comment that ruthenium showed little tendency to deposit anywhere in the body, and tended to be excreted almost as fast as it was absorbed from the lungs. They also noted that urine and feces carried about equal amounts with the possibility of a difference between vapor and aerosol.

In the same report, Abrams describes the progress with three-hundred-day cerium. Here a dc arc was used, and an average dose of about 50 μ Ci per animal was given. There was extensive respiratory involvement in enough of the animals that it was concluded this dose was near the LD₅₀ (or what they termed the SD [sick dose] 50).

Abrams and Seibert reported on effects of fifty-seven-day yttrium inhaled as an atomized aqueous solution some seven months before. There was no evidence of damage, even though the initial lung dose was 26 μ Ci. The material was eliminated very rapidly, and the calculated lung dose was about 1,500 roentgens. They turned, instead, to a dc arc in hope of obtaining a more insoluble material. They put 400 mCi of the radioisotope on the electrodes of the arc to accomplish this exposure.

The first major summary of the inhaled longer-lived fission product work came in April 1946. This was a 109-page document that describes work with strontium, zirconium, yttrium, and cesium (Abrams et al. 1946d). It is noted that the work began before the Clinton Pile was in operation, but continued and grew as materials became available. The elements chosen were considered as representative fission products, and all were carrier-free. The report is presented as a chronology, with techniques and their evolution described in each section. A useful feature is the depiction of the fission product chain producing

the given element with half-lives and maximum energy. The strontium isotope was ^{89}Sr , the zirconium isotope ^{95}Zr , the yttrium isotope ^{91}Y , and the cerium isotope primarily the ^{144}Ce - ^{144}Pr couplet. With the exception of strontium, each radioisotope was presented as both a soluble aerosol, from atomization of an aqueous solution, and an insoluble aerosol prepared by burning in the carbon arc.

There were significant differences in behavior among these four elements, particularly between strontium and the other three.

It is expedient to summarize this by extracting from the abstract of the report:

Strontium differs from the other elements investigated in the ease with which it is absorbed from the lungs. Over 50 percent left the lungs within a matter of minutes, and 95 percent was gone within 1 hour. Of the Sr^{89} originally in the lung, 60 percent was deposited in the skeleton in less than 4 hours, and after 12 hours the total radiation dose to the skeleton exceeded that to the lungs. These results indicated that inhalation was as effective a means of administration as intravenous injection, and that lung damage as a result of inhalation of Sr^{89} would be of less importance than bone marrow damage.

The other three elements, Y, Zr, and Ce, may be grouped together insofar as they differ from Sr. They were all eliminated from the lung much more slowly than was Sr. Thus the times required for 90 percent elimination were: Y^{91} , 12 days; Zr^{95} , 25 days; and Ce^{144} , 45 days. In all cases the skeleton was the major site of deposition and eventually contained between 15 and 30 percent of the initial lung deposit. In no case, in periods ranging up to 200 days, did the total radiation dose to the bone exceed that to the lung, as it did within 12 hours with Sr. With all three elements the probability of radiation damage to the lung is great.

Very little deposition occurred in the soft tissues. The kidney contained about 0.5 percent of the dose with all the elements. Concentration in the liver was lower than in the kidney with all isotopes except Ce^{144} . This element showed a very high initial liver deposition, but this was gradually eliminated so that after 2 months the liver concentration fell below that in the kidney.

(Abrams et al. 1946d)

Integrated radiation doses were calculated where feasible. The dose to femur exceeded that to lung within ten days after ^{89}Sr administration. The metabolism data indicate that this might be true also for ^{91}Y , probably only true after longer times for ^{95}Zr and never for ^{144}Ce .

Differences between soluble and insoluble forms were expressed largely in slower elimination from the lungs of the insoluble form. Once absorbed, there was little difference in subsequent tissue distribution. An example of the difference in lung clearance seen with the two forms of ^{95}Zr is shown in figure 9.6.(a)

The very large amount of cerium deposited in liver as compared to the other elements is worthy of note. This was seen also in the Berkeley work.

Autoradiographs of lung and bone were made in a few instances. However, the authors do not remark upon these in detail, and the reproduction makes it difficult to analyze them independently.

Although the metabolism work extended to thirty days, there does not appear to have been any attempt at histopathological examination, or any chronicling of biological effects. It is concluded, nevertheless, that the danger of damage to the lung probably exceeds that to other tissues in these types of exposure.

(a) The number of experimental points shown in figure 9.6 reiterates the fact that much of this wartime inhalation work was range-finding in nature. The tabular material is usually more detailed than the items chosen to present in graphs.

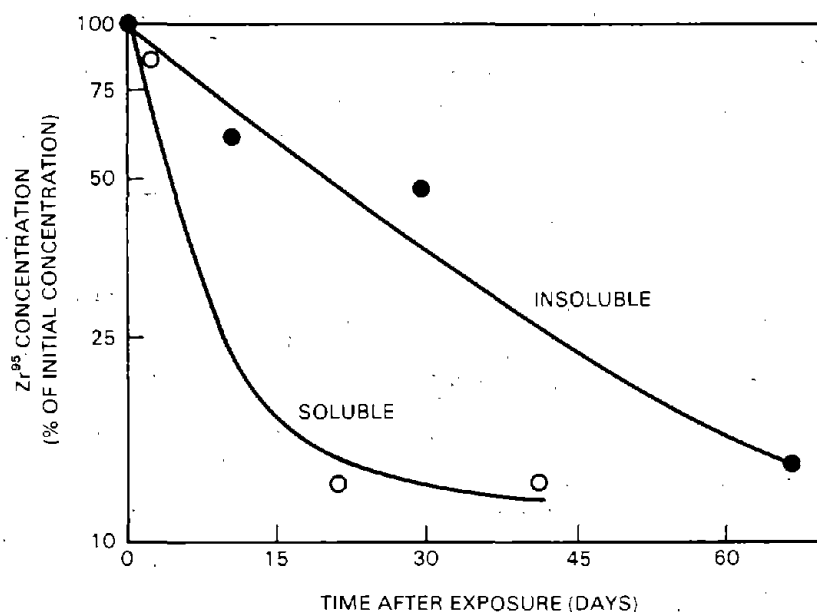


FIGURE 9.6. Relative rates of elimination of ^{95}Zr from the lung following inhalation of atomizer ("soluble") aerosol and arc ("insoluble") aerosol. (Redrawn from Abrams et al. 1946d.)

A frank effects study on a long-lived fission product is seen in an undated report by Seibert and Abrams. (Since it was declassified in September 1946, it could not have been produced later than 1945, and is so referenced.) This work of Seibert and Abrams (undated) concerned the acute toxicity of 275-day ^{144}Ce . Fairly large groups of rats were exposed to smokes produced by the arc technique using tracheal cannulation. There were five groups that received doses of 3.2, 14, 39, 50, or 200 μCi per rat. All but one group utilized the exposure apparatus described in section II C 2. Weight loss was significant only at the highest exposure, and these animals had a median survival time of 39 days. The median survival time at the level of 39 μCi per rat was 282 days, while 90% of the animals given 14 μCi were alive at 300 days.

The distribution in lung of ^{144}Ce was quite irregular in contrast to zirconium, and it was also irregular in the liver. On the other hand, cerium was distributed throughout bone cortex in contrast to zirconium and plutonium.

Acute inflammatory reactions were described in lung, but they were variable in both extent and progression with time. Cervical lymph nodes and the tip of the spleen nearest the lung showed direct effects similar to external radiation. Both thymus and spleen showed cellular depletion. There were small changes in bone marrow and kidney, practically no changes in liver, heart, adrenals, gut, and pancreas. Some squamous proliferation of bronchial epithelium was noted.

Radiation doses were calculated to the several tissues and compared to the dose of external radiation with which the observed effect could be associated. No differences appeared that would correlate death with dose to any single tissue, although obviously the lung was a prime candidate.

A study reported in 1945 on 1.0-yr ruthenium can close our consideration of the Chicago work with inhaled long-lived fission products. This is termed a tracer study, but actually concerned chemical toxicity as well as distribution and excretion of the radioisotopes.

The abstract of this report reads as follows:

This paper deals primarily with the fate of tracer quantities of airborne ruthenium after inhalation by rats.

1. In the course of the work it was necessary to have a simple, quantitative test for Ru, and a colorimetric test was developed which depends on the blue color formed with rubeanic acid. It was possible to detect 2 μg of Ru with 10 percent accuracy.
2. In order to expose animals to RuO_4 vapor, a generator was needed which would supply RuO_4 at a continuous and more or less uniform rate. Of a number of oxidizing agents investigated for this purpose, potassium permanganate in sulfuric acid was best suited.
3. A rough determination was made of the chemical toxicity of Ru for mice. By intracardiac injection, doses in the range of 3 $\mu\text{g/g}$ were acutely toxic.
4. Methods have been developed for assaying tissues for radioactive ruthenium. The hard β of the 1.0 year Ru - 30 sec Rh system is counted. To avoid volatility losses, small tissues are minced, dried at 110°, and counted. Larger tissues are muffled and a correction made for losses due to volatility.
5. Three types of Ru exposure were carried out: to RuO_4 vapor, dry " RuCl_3 " aerosol, and " RuCl_3 " solution. In all cases the Ru was rapidly absorbed from the lungs and rapidly excreted via the urine and feces. The kidney tends to retain a considerably higher concentration than other tissues. The rapid excretion, approximately 90 per cent in 30 days, minimizes the hazard resulting from internally deposited Ru.

(Dailey, Wender, and Abrams 1945)

This work appeared piecemeal in many monthly reports and is probably chronologically older than much of the other Chicago work cited in this section. It gives an excellent review of the properties of stable ruthenium and ruthenium tetroxide, radiochemical properties of the several isotopes, a colorimetric method for quantitative analysis of stable ruthenium, and the distribution of the one-year isotope in the tissues of rats. The problems of devising atomizers and chambers are also included, and the study is topped off by exposure to a " RuCl_3 " solution by intubation. They conclude that it is the one-year ^{106}Ru + rhodium daughter couplet that is most important energetically. However, because of very rapid excretion, hazards from internally deposited ruthenium of the types used in these experiments were considered minimal when compared with other fission products. The presence of a significant potential for chemical toxicity is worthy of note, and the Chicago workers deserve kudos for investigating this often neglected possibility with radioisotopes, even though it does not control in this particular instance.

5. Plutonium

Inhalation work with plutonium at Chicago developed more slowly than the work with fission products. This was partly because of the lag in availability of the element (see chapter 7) and partly because of the disheartening technical problems of producing useful aerosols of plutonium, discussed briefly in section II C 2 above. The monthly reports seen in Dr. Abrams's file (cf. section II C 1) mention plans for inhalation experiments with plutonium as early as June 1944.

This was only a few months after allocation of the 10 mg of precious cyclotron-produced plutonium to Joe Hamilton at Berkeley in late January 1944. In July 1944, a note is made of attempts to work with dry plutonium as the cupferron complex, and aerosol production by a Freon bomb technique is described. By August, the influence of valence state is mentioned. Nevertheless, the problems of getting a plutonium aerosol produced with sufficient efficiency to allow studies of biological effects and reproducibility predominated these progress reports.

By January 1945, enough tracer work was done to allow concluding that the valence IV state remains in the lung much longer than either valence III or valence VI. In February, they reported on arc-produced aerosols of a zirconium-plutonium mixture, on the large effect of complexing with citrate, and they drew the conclusion that the nature of the inhaled compound can have as much effect on distribution as the mode of administration itself. In the spring of 1945, the metabolism of plutonium was followed up with the conclusion that valence IV plutonium could remain in the lung for long periods, with major deposition sites after absorption being the liver and skeleton. This latter allowed some tentative cross-correlations between these inhalation experiments and the further-advanced intravenous work at Chicago and elsewhere.

However, even in spring and summer 1945, when the Chicago workers wanted to place a known dose of plutonium in the lung, they resorted to intratracheal intubation (instillation). A complete report prepared for the PPR^(a) volumes draws all of this work together (Abrams et al. 1946b). It brings in Herman Lisco as pathologist and Leon Jacobson as hematologist, names we have already seen associated with much of the biomedical effort at Chicago in chapters 6 and 7. Their presence meant that the aerosol people had finally gotten effects. Even though the short-circuit route of intratracheal administration is not a perfect substitute for inhalation, the results were important.

First, the tight binding of plutonium in the lung was found to occur also after this mode of administration. A quarter of the dose was still present after 210 days.

Second, the skeleton retained the major portion of the plutonium that left the lung via the bloodstream.

Third, damage to the lungs was extensive and considerable. The doses ranged from 7.5 to 500 μg per 200-g rat (0.5 to 31 μCi per rat). Even the lowest dose produced progressive pulmonary damage, characterized by inflammation, necrosis, and abscess formation. Animals surviving a month or longer showed persistent, acute and chronic inflammation; emphysema; and in many animals "a striking squamous metaplasia of the bronchial epithelium which often showed remarkable proliferative activity."

Fourth, toxicity of plutonium entering by the lung appeared significantly greater than the same dose given intravenously. Table 9.1A, taken from the Abrams et al. (1946b) paper, illustrates this point, and table 9.1B shows the calculated radiation doses to lung and skeleton.

Note that the difference between intrapulmonary and intravenous toxicity increased with time. The "median lethal doses" in table 9.1B are expressed in terms of the organ concerned and thus vary with plutonium content of the organ. They are probably not very meaningful, except to show the very large radiation dose imparted to lung and that lung dose exceeded bone dose by a

(a) Plutonium Project Report, the earlier name for the NNEs volumes.

TABLE 9.1. Acute Toxicity of Plutonium by Intratracheal Instillation in the Rat

A. Median Lethal Dose (LD₅₀)					
	Time After Administration (days)	Median Lethal Dose ($\mu\text{C/g}$)			
		Intrapulmonary	Intravenous		
	30	0.081	0.062		
	60	0.025	—		
	90	0.013	0.062		
	150	0.006	0.050		

B. Median Lethal Dose, Δ_M					
Dosage Group	Dose ($\mu\text{C/rat}$)	Median Survival Time (days)	Δ_M , Lung (rep)	Δ_M , Skeleton (rep)	Lung/Bone
A	0.5	203	2,600	340	8
B	1.5	154	7,200	720	10
C	4.3	67	15,000	570	26
D	13.00	24	29,000	310	93
E	31.00	26	72,000	840	86

Source: Reset from Abrams et al. 1946b.

Note: The "rep" unit was used for several years for situations in which the roentgen did not apply. The letters stood for "roentgen equivalent physical." For our purposes, we can equate it approximately, but far from exactly, to the rad.

factor of eight, even at the lowest level. It was over eighty times the bone dose at Level E.

This experiment was probably the first to highlight the special effectiveness of plutonium in producing lung damage. We will see the same general phenomenon in the postwar work where carcinogenesis is the primary criterion.

The authors speculated that the consolidation, hypertrophy, and abscesses in lung contributed to the high retention of plutonium. While this was undoubtedly true, later work at lower concentrations exhibited avid lung retention without such extensive pulmonary damage.

There was very little deposition in liver in these intratracheal intubation experiments.

The pathologic changes in tissue other than lung were inconsequential relatively, although significant hematological changes occurred in the groups receiving 24 and 70 μg per rat (observations began approximately fifty days after administration). The dose of 7.5 μg per rat produced no significant deviations from normal over a two-hundred-day period. The changes, when seen, involved moderate anemia, preceded sometimes by an initial elevation in erythrocyte count, plus the usual decreases in lymphocytes with return toward normal at the intermediate doses. The hematological effects were less marked than those following equivalent doses given by either the intramuscular or intravenous routes. This difference was attributed to the retention in lung and lesser participation of this plutonium in the production of hematological changes.

The high retention in lung and the extent of damage produced therein are held responsible for the high lethality of plutonium in this experiment.

The 1945 monthly reports contain increasingly frequent reference to true inhalation experiments with plutonium, primarily experiments on metabolism. Something must have begun to go right with aerosol techniques for plutonium, or the investigators decided to go ahead with what they had. The efficiency remained low, but plutonium was no longer scarce, and they could thus afford larger initial quantities. Unfortunately, the accuracy and reproducibility of the dosage never even came close to the intratracheal intubation technique. Yet, the noted differences in deposition kinetics and subsequent tissue distributions between inhalation and intubation made experiments with inhaled aerosols essential.

The bulk of the Chicago experimental work on inhaled plutonium is contained in a report prepared in October 1946 by Abrams and colleagues (1946c). This manuscript was slated for one of the PPR volumes (NNES) that was not published (Appendix C).

The source of the plutonium was given as the Chemistry Division of the Metallurgical Laboratory. It very likely came from a reactor at Clinton Laboratory.

Nearly all of the exposure techniques described by Abrams et al. (1946a) were used. These were basically atomization of the soluble forms and development of oxide smokes either in a carbon arc or by exploding a plutonium metal foil wrapped in thin aluminum foil by a high-energy condenser discharge.

This was all distribution and excretion work using primarily the rat. The system never reached the point of permitting effects levels on inhalation of plutonium. The chief virtue of this work is the increase in numbers of experiments and numbers of points per experiment so that the major findings can be considered dependably demonstrated. Effects of valence state were confirmed. Even using "soluble" aerosols, tetravalent plutonium was comparable to the most insoluble of the fission products. Indeed, elimination from lung seemed to cease altogether after about two months, with about 10% of the initial dose tightly bound. Plutonium (VI) showed an initial period of rapid loss, but after about five days behaved like plutonium (IV). It was postulated that the VI state was converted to the IV state *in vivo*, a conclusion that has stood the test of time.

Skeleton, the major site of deposition of absorbed plutonium, carried about 20% of the initial dose. Unlike the findings with parenteral routes of entry, the liver did not usually even approach skeleton in content, either early or late. In fact, liver and kidney were close together in most cases. With plutonium (III) given as the nitrate, liver was slightly higher than kidney. However, none of the results showed the almost equal division of plutonium between liver and bone described in postwar work using the parenteral route of entry.

The second major set of experiments with inhaled soluble plutonium at Chicago concerned the effect of complexing. The agents used were cupferron, citrate, and Calgon (a metaphosphate detergent of the day).

Cupferron had relatively little effect on the rate of elimination from the lungs, but it did have a striking effect on skeletal retention, i.e., 7% at 110 days versus 20% in the absence of complexer. Also, absorption seemed to be poorer. Both of these earmarked cupferron as a possible therapeutic agent for plutonium poisoning. However, this idea seems to have fallen by the wayside.

For the study of citrate and calgonate, the investigators returned to intratracheal intubation because they wished a "more reproducible initial dose." Citrate had dramatic effects. Plutonium citrate was even more mobile than the

soluble nitrate salts. Indeed, combining with citrate had effects that outweighed differences in valence so that Pu (IV) and Pu (VI) citrate behaved quite similarly. Deposition of the citrate in both skeleton and liver was rapid and large. The deposit in liver left quickly, however.

Calgonate was not a particularly effective complexing agent in terms of its effect on tissue distribution after intubation.

The inhalation of plutonium oxide smokes did not add much new to the story that was not already known from other sources. However, the experiments were the longest reported in the Manhattan District inhalation series at Chicago; they extended to a full year. They demonstrated clearly the continued extreme insolubility of plutonium-oxide and almost quantitative deposition in the lung and upper respiratory tract. Since the particle size was quite small, nearly all of the smoke was of respirable particle size. Soft tissues accumulated negligible quantities. There was, however, considerable elimination from lungs after these smoke depositions, and significant, though not large, transfer to skeleton.

The figures, given as percent of initial dose per organ or as percent of initial dose per gram of tissue, are shown in table 9.2A and B.

TABLE 9.2A. Distribution of Inhaled Plutonium Oxide in the Rat

Time After Exposure (Days)	0	10	29	66	124	202	364
Tissues	Tissue Content (Per cent of Initial Dose)						
Lung	99	96	46	24	32	8.5	6.2
Trachea	1.3	0.3	0.2	0.2	0.5	0.5	0.7
Kidney	0.12	0.07	0.09	0.15	0.04	0.06	0.03
Liver	0.10	1.04	0.50	0.15	0.23	0.27	0.11
Spleen	0.10	0.08	0.08	0.06	0.03	0.05	0.06
Skeleton	0.42	6.2	6.2	3.8	7.0	3.3	6.2
GI-tract	0.15	2.1	1.0	1.3	0.15	0.09	0.04

TABLE 9.2B. Tissue Concentration of Inhaled Plutonium Oxide in the Rat

Time After Exposure (Days)	0	10	29	66	124	202	364
Tissues	Tissue Content (Per cent of Initial Dose per g)						
Lung	58	71	30	22	25	6.2	2.3
Trachea	9.2	1.5	2.5	2.3	2.5	1.9	1.4
Kidney	0.06	0.04	0.05	0.09	0.03	0.04	0.01
Liver	0.01	0.11	0.05	0.02	0.03	0.03	0.01
Spleen	0.07	0.23	0.13	0.12	0.06	0.11	0.15
Skeleton	0.02	1.4	0.35	0.11	0.32	0.17	0.25
GI-tract	0.01	0.10	0.03	0.01	0.01	0	0

Source: Reset from Abrams et al. 1946c.

These figures should be kept in mind for comparison with the more sophisticated postwar experiments since the smoke form may well be more likely encountered in occupational or accidental exposures than aerosols with larger mean particle sizes.

The feces were the main route of excretion. It is of interest that the fecal excretion rate, up to eighty-four days at least, corresponded closely to the rate of elimination from the lungs. The very much lower urinary excretion rate seemed to parallel the loss rate from liver. This, too, should be earmarked for comparison with later work by both inhalation and other routes of entry.

Quite logically, Abrams et al. conclude that the smoke is predominately a hazard to lung, whereas the hazard to lung from "soluble salts like the nitrate is distinctly less." Since no formal effects studies were done in the plutonium inhalation experiments, the possibility of bone damage could not be checked out. However, the concentrations in skeleton after inhalation of the soluble salts bespeak the possibility of biological damage.

6. Histopathological Data from Bloom

Bloom received a few specimens from the inhalation experiments for histopathological examination. The paragraph concerning the inhalation work, which appeared in the chapter on lung in his classic book in the NNES series (Bloom 1948), is reproduced below. Note that it includes plutonium.

A few rats were available for the study of lung tissue after inhalation of yttrium 91, cerium-praseodymium (275-day), or plutonium. Control rats were divided into two groups. Both groups were given an anesthetic, and cannulas were inserted into the tracheas of the second group only. Experimental rats, in addition to the anesthetic and the cannula, received 28 or 220 microcuries per rat of yttrium 91 (AY), 50 microcuries per rat of cerium-praseodymium (275-day) (ACB), or 1.5 to 31.5 microcuries per rat of plutonium (APME). Seibert and Abrams discuss the probable distribution of inhaled particles of cerium-praseodymium and plutonium. The experimental animals showed effects similar to those seen in the controls, with a further striking reaction of the bronchiolar epithelium. In the experimentals the regrowth was more extensive. Although in the yttrium 91 and cerium-praseodymium (275-day) series the epithelium did not go beyond the confines of the basement membrane, many bronchioles contained several layers of spindle cells. Some of these grew with their long axes surrounding the vessel, and in other areas there seemed to be no orientation. In a specimen from a rat sacrificed one month after inhalation of plutonium, the growth of epithelial cells appeared suggestively neoplastic (Figs. 15.1 and 15.2). One of the three rats killed six months after inhalation of cerium-praseodymium (275-day) appeared normal; the other two contained extensive epithelial cell proliferation. Whether the final disposition of these cells is toward cancer or the normal condition cannot be stated. However, it is certain that these animals reacted positively in their bronchiolar epithelium to the inhalation of radioactive materials. The reaction was more extensive and for a longer period than the reaction of those animals exposed to nonactive substances.

(Bloom 1948, pp. 707-708)

7. Recap of the Chicago Inhalation Studies

The rather considerable amount of work done on inhalation of fission products and plutonium at both Chicago and Berkeley did not have the same impact on the field as the parenteral administration work reviewed in chapters 6 and 7. This was partly because of the technical difficulties and the lower degree of confidence in the results that this engendered in the investigators themselves. It

was partly due to the fact that less work was done. Reviewed in light of the enormous postwar enterprises, the results are not all that bad. They established a firm beachhead and pointed the way with general conclusions that have stood up.

A significant point of contrast between inhalation and parenteral administration seen in this work is, besides the obvious involvement of lung, the small amounts of plutonium deposited in liver.

D. Inhalation Work at Rochester

Two completely separate sets of inhalation experiments were carried out at the University of Rochester School of Medicine and Dentistry during the Manhattan Project days. They were in separate divisions of the project. Because of the tight security, the work and reports thereon were almost completely isolated from each other, although it seems unlikely that the large installation of exposure chambers could have been completely isolated and unnoticed. The work involved inhalation of smokes of ^{210}Po on the one hand, and the inhalation of uranium dusts and gaseous uranium compounds, such as the hexafluoride, on the other hand.

1. Work with Polonium-210

This work was carried out under the Biological Chemistry Section of the Division of Radioactivity in the Manhattan Department of the University of Rochester.^(a) It was reported in classified reports and in the NNES volume edited by Robert Fink (Fink 1950) and was part of the major effort on alpha-emitting radionuclides discussed in chapter 4 of this book. The authors of the inhalation section are C. P. Kimball and R. M. Fink (Kimball and Fink 1950).

A technique generically similar to that used for producing fission-product and plutonium smokes at Chicago and Berkeley was employed, but with differences in detail. All exposures involved evaporating a droplet of polonium onto a nickel foil, which was heated by passage of an electric current until it burned out. Since polonium is quite volatile, there were few problems with the efficiency of aerosol production, although there is no doubt that appreciable quantities plated out in the apparatus. No particle size analyses were made. The technique used for generating smokes usually produces relatively small particles.

There were two systems set up for nose-only exposure to volatilized polonium entrained in an air stream. The first was a straight-through system attached to a suction sump. The second was a closed system of small volume. These are pictured in the cited reference (Kimball and Fink 1950) as figures 2.28 (p. 90) and 2.31 (p. 97). In both, the rat's snout was in fairly close proximity to the foil.

The third system was a somewhat heroic attempt to separate inhaled from exhaled air in order to measure directly the amount of airborne polonium exhaled and to compare this with the amount deposited in the body. Dead space in this system was nil since both ingress and egress were through nasal cannulae. One cannula was inserted in one nostril and one in the other. The experiment was done under deep anesthesia. There were two versions of this system, but neither worked very well. The cannulae easily became plugged with

(a) Remember that the Rochester Project was not part of the Metallurgical Laboratory portion of the Manhattan District Corps of Engineers.

nasal secretions, and it was difficult to get sufficient air through the system. The results were quite variable. Initial deposition was predominantly in the lungs using the straight-through apparatus, about equally divided between lung and nasal passages with the closed system. Amounts in selected tissues at twenty-four hours and ten days after administration are shown in table 9.3 using data from the more extensive tables in the Fink volume.

TABLE 9.3. Amount of Polonium in Tissues After Inhalation. Average of two rats. Percentage of dose.

Tissue	24 Hours		10 Days	
	Whole Tissue	Per Gram	Whole Tissue	Per Gram
Lungs	30.4	20.1	5.5	4.6
Intestine	18.6	2.7	3.1	0.2
Skin from head	12.8	4.0	0.8	0.4
Skin, except head	5.9	0.1	3.9	0.1
Nasal Passages	1.4	0.2	1.6	0.5
Oral Passages	0.2	0.05	0.7	0.2
Kidney	1.2	0.7	3.2	1.8
Spleen	0.7	0.8	2.2	2.3
Blood Cells	2.9*	0.4	0.6	1.0
Bone	1.8	0.07	2.4	0.1
Liver	1.4	0.2	4.3	0.5

*One rat only.

Source: Reset from tabular data given by Kimball and Fink 1950.

Note: Numbers have been rounded off.

As might be expected, lung tissues are far ahead of others at twenty-four hours and maintain the position of having the most polonium at ten days, but not by such a large margin. Note that the *concentration* (percentage of dose per gram) rises significantly in kidney, spleen, and blood cells between one and ten days.

Since a primary point of interest in doing these experiments was to ascertain the tissue distribution of polonium entering from the lung compared to other routes of entry, a comparison has been put together as table 9.4.

TABLE 9.4. Percentage of Dose Per Gram of Polonium in Selected Tissues of the Rat

Tissue	24 Hours		10 Days		
	Inhalation	Intravenous	Inhalation	Intravenous	Oral
Lungs	20.1	0.9	4.6	0.8	0.03
Intestine	2.7	0.7	0.2	0.6	0.01
Kidney	0.7	3.6	1.8	4.3	0.05
Spleen	0.8	5.1	2.3	9.3	0.1
Blood Cells	0.4	2.3	1.0	1.2	0.2
Bone	0.07	0.4	0.1	0.4	0.01
Liver	0.2	1.7	0.5	1.3	0.01

Source: Reset from numbers in Kimball and Fink 1950.

Note: Averages have been rounded off.

These are concentrations (percentage of dose per gram of tissue). Note that differences appear between inhalation and intravenous routes in kidney, spleen, liver, and blood cells, as well as lung, at both one and ten days. The figures for oral administration are complicated by the fact that there is far from complete absorption of the administered dose from the gastrointestinal tract (see chapter 4).

It can be speculated that polonium entering the blood stream from lung is more likely to be monatomic, or at least in much less aggregated form than that entering via intravenous injection. The considerable amount of colloidal or semicolloidal material present after intravenous administration is taken up by the reticuloendothelial system (RES) cells in spleen and liver.^(a)

Thus, at least up to ten days, there are some quantitative differences in the tissue distribution of inhaled polonium versus injected or ingested. Nevertheless, the investigators were more impressed with the similarities than the differences among the routes of administration, except for lung. Furthermore, it appears that volatilized polonium, presumably an oxide, is largely absorbed into the blood stream from the lungs, but that a small fraction remains as noted below.

An experiment was conducted specifically to determine loss rates from lungs and upper respiratory passages. Instead of nose-only exposure, this experiment was done in a large chamber (glass jar) which would allow simultaneous exposure of fifteen to twenty rats. The results, shown in figure 9.7, were unexpected. Although clearance was initially rapid from all the sites measured, an appreciably greater amount remained in lung than in upper respiratory passages or on the skin of the head.

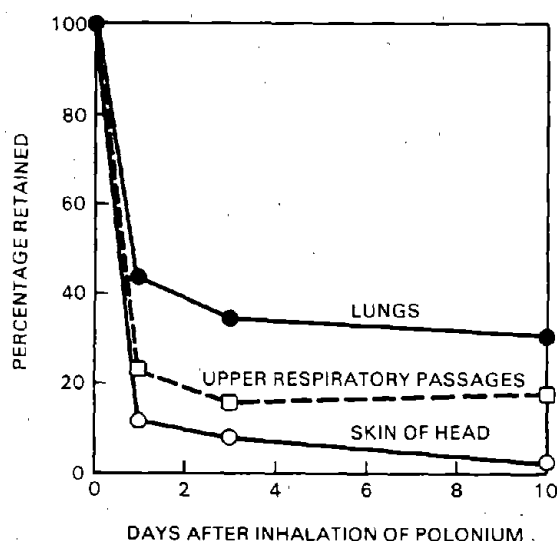


FIGURE 9.7. Retention of polonium deposited in lungs, upper respiratory passages, and skin of head of rats after exposure to volatilized polonium. (Redrawn from Kimball and Fink 1950, p. 108.)

(a) The kidney and blood cell concentrations represent other processes (chapter 4).

These results are reminiscent of the phenomena seen with insoluble oxides of plutonium and fission products. They suggest that even relatively soluble materials, such as most of the compounds of polonium, can be bound in lung moderately tightly.

Excretion was measured by putting a few animals in metabolism cages. Average cumulative excretion of inhaled polonium in urine, over a ten-day period, was 3.1% of dose after inhalation, only 0.8% of dose after intravenous administration, and 2.1% of dose after oral administration. Ten-day totals for fecal excretion were 66.1% of dose after inhalation, 25.2% after intravenous entry, and 98.6% (a) after oral administration.

Calculations of total absorption indicated that more polonium is absorbed from the lung into the blood stream than after administration of a comparable amount by stomach tube.

Autoradiographic pictures were made of volatilized polonium in the lungs. These showed, initially, fairly uniform distribution in alveolar tissues, except toward the outer borders of the lobes. Bronchial linings showed clearly. By twenty-four hours, only a little polonium was left on the bronchial walls, while the location of dense activity had spread slightly farther into the alveolar tissues.

The Rochester work with inhaled polonium did not carry beyond ten days or into the realm of effects. There were relatively few animals. They were exposed individually, except for the one experiment to determine respiratory-tract loss. The amounts of polonium deposited in the animals varied from animal to animal sufficiently to discourage attempts at setting up any study of effects. They do, however, suggest that inhaled polonium will, except for the involvement of lungs, distribute qualitatively like material received intravenously, but with some quantitative differences.

Again, as in the work at Berkeley and at Chicago during these wartime years, relatively little is said about the safety precautions instituted in generating these smokes. However, the exiting air streams were usually bubbled through from one to several wash bottles in tandem. Polonium is soluble enough in the acid used in the open-end system, or strong alkali used in the closed system to absorb CO_2 , to make it unlikely that significant quantities got out of the apparatus.

2. Uranium

The work at Rochester on inhalation of uranium, under the Manhattan Project, concentrated on compounds of natural uranium. An overview of the entire program is given in chapter 2, including details of the long-term postwar experiment. The MED work was presented in depth in four book-length reports in the National Energy Series (hereafter called "The Uranium Monograph"). It was in two distinct sections, one published in 1949, the other in 1953.

The methodology for inhalation exposures differed from that used at Chicago and Berkeley and for the polonium work at Rochester in that it could draw much more upon the fast-developing field of industrial hygiene than could the methods used for the more highly radioactive materials. Dust feeds and relatively macro amounts of material could be used. Analyses were largely by

(a) The fact that urine and feces account for over 100% of the dose in this case is within experimental error and reflects the relatively poor absorption from the gut.

chemical methodology rather than radioactivity. The biological endpoint was chemical toxicology, primarily kidney damage, with some lung damage at high concentrations.

a. Development of the Program

The Manhattan District Corps of Engineers and its predecessor organization, OSRD,^(a) were convinced from the start that some of their earliest health problems might center around the handling of uranium. After all, uranium ore had to be treated and several compounds made before any of the next steps in the development of the project could proceed. Also, they were convinced that the prime route of entry would be inhalation.^(b)

As soon as the Rochester Project was organized, a program was mapped out to do inhalation toxicology on twelve different uranium dusts (eleven different compounds and one ore dust), and to ascertain very acute toxicity (one day), acute toxicity (thirty days), and longer-term or chronic toxicity (one year). All exposures were continued for the period named. Effects were observed over longer periods in some instances.

The background against which this ambitious program began is described quite clearly in the beginning of the inhalation toxicology chapter in the first of the NNE monographs by Voegtlin and Hodge (1949). There was essentially no previous information available on inhalation of uranium dusts per se.

The pressures to learn something were tremendous. Work began almost immediately. An example of some of the crude experimental beginnings was given in chapter 2.

In January 1944 (the project began in spring 1943), it became apparent that the buildings, equipment, and personnel could not begin to keep pace with the urgent health problems expected to arise in the handling of uranium or even with the fast-developing requirements of the experimental regime itself.^(c) Approach to longer-term toxicity studies seemed as far away as it had at the outset of the work. Yet, this was one of the chief concerns. Important decisions had to be made. These were as follows:

1. The acute, chronic, shorter-term, and longer-term exposures would be done as nearly simultaneously as possible rather than awaiting the results of one before proceeding to the next. Also, some planned experiments on acute toxicity would be omitted.
2. A new wing was to be constructed on the project buildings, largely to accommodate exposure chambers, additional personnel, and animal care facilities. This additional facility is the one-story building at the right of the picture of the early Rochester Project building shown in figure 2.1 of chapter 2. It was quite deep and contained a surprising amount of space.
3. On completion of the new facilities, the entire operation was to go on a two- or three-shift-per-day basis. This involved not only the exposures, but the supporting and collaborating functions, such as hematology, pathology, analytical chemistry, biochemistry, physiology, surgery, statistics, etc.

(a) Office of Scientific Research & Development

(b) Remember the "Green Hornet" we met in chapter 2.

(c) Additional work involving toxicology of fluorine and of special materials related to the toxicology of uranium had been piled onto the already overwhelming burden.

4. The staff was augmented by assignment of many additional military personnel who had from considerable to essentially no training in science, as well as by recruitment of civilian scientists wishing to contribute to the war effort.
5. Frequent joint planning sessions and conferences were held. Each exposure study was carefully examined and planned, both by discussion and by circulation of detailed memoranda.^(a)
6. Personnel were divided into teams around each animal-exposure unit, with a Ph.D. biomedical scientist in charge, who was aided by three to five assistants with M.S. or B.S. degrees. Only the animal care away from the chambers devolved on other personnel.

As a result of this semimilitary organization^(b), important data began to accumulate quite rapidly and, thanks to a laudable compulsion for follow-through on the part of Harold Hodge, Herbert Stokinger, Aser Rothstein, C. W. LaBelle, and many others mentioned as authors of the Inhalation Toxicology chapter in the NNEs monograph, the goals were reached. Not only were the experiments completed, but the strengths and weaknesses of inhalation work were carefully analyzed.^(c) While numbers do not guarantee quality, it is impressive to note that during the three-year inhalation program at Rochester, more than twelve thousand animals were involved. Seven species contributed: rats, dogs, rabbits, guinea pigs, mice, cats, and hamsters. This array was, of course, far beyond anything possible in the programs with smokes and mists described earlier in this chapter. Indeed, it suggests the need for some sort of memorial to these thousands of animals that contributed in their way to the war effort.

b. Exposure Chambers

The chamber designs for the Rochester uranium work leaned toward large size. They were, after all, looking for effects in addition to distribution and excretion and needed to expose significant numbers of animals for each run. Nevertheless, they utilized both the nose-only mode and whole-body exposure. The design was based in part upon a survey of installations at the Dow Chemical Company, the National Institute of Health of the U.S. Public Health Service, the Kettering Laboratories, and the U.S. Bureau of Mines, but they soon assumed characteristics and identities of their own.

The Rochester chambers ranged downward in size to two all-metal construction units donated by the University of Pennsylvania for special tests. Materials varied from wood and glass with transite lining, through wood-framed metal units, to all-metal units for the more corrosive dusts and vapors such as uranium hexafluoride.

Naturally, chambers of this size could be used only with a relatively abundant material of low specific activity, such as natural uranium. Uniformity of distribution of the aerosol within the chamber was a major engineering challenge. It seems to have been met adequately for the work at hand. Details of the cage racks, rubber neck-gaskets, etc. are given in the published monographs. Despite appearances, these exposure rigs were relatively comfortable for the animals, who would frequently sleep during the exposure.

(a) Security could be kept by utilizing code names and numbers in any general conference and in the written documents.

(b) Further details can be seen in chapter 10 of Voegtlin and Hodge (1949).

(c) As we saw in chapter 2, much besides inhalation work was going on, but the chapter describing it is by far the longest in the monograph (277 pages).

c. Dust Feeds and Sampling

A variety of dust feeds were tested out before exposures since the properties of the twelve uranium compounds varied considerably. There was a pressure feed device (figure 10.6, chapter 10, Voegtlin and Hodge 1949), which had the same principle as some of the mist generators, described earlier, but which introduced solid material to the air stream. A modification of this was a ball-mill dust feed, which ground the powder in situ just before it was taken into the air stream to the exposure chamber (figure 10.7, Voegtlin and Hodge 1949). An agitated illutriator reminiscent of the device developed at Chicago worked quite well on dry dusts (figure 10.8, Voegtlin and Hodge 1949). Feed systems for UF_6 had to handle and introduce a corrosive vapor. The prime need here was exclusion of all possible water vapor (figures 10.9-10.11, Voegtlin and Hodge 1949).

Dust concentrations produced by these various methods were established in most studies by a filter-paper dust sample run at constant air flow. This sampler was modeled after the unit being used at the National Institute of Health, Division of Industrial Hygiene, by L. T. Fairhall and colleagues (for example, Fairhall and Sayers 1940). It was modified so that samples could be taken at any location in the chamber, rather than just at the wall of the unit. This allowed checking the uniformity of distribution of the dust. The samples were subjected to chemical analysis, and frequency-distribution curves of dust concentration were plotted. These showed the mean level, its relation to the desired level, and the distribution of points for both low-level and high-level exposure modes. In general, the range was smaller around the lower-level mean than around the higher-level mean. This information was essential for effects studies where the occurrence of pathologic responses some months hence was in question.

d. Particle Size Determinations

The Rochester investigators put a tremendous effort into both determination of particle size and studies of the effects of particle size. This went far beyond the consideration given to particle size in either the Berkeley or the Chicago work. This was partly because they were using by and large true dusts with a considerable range of particle sizes and, thus, also of relative respirability, and partly because the larger amounts of material made such work more feasible.

They looked at the air centrifuge, the photographic ultramicroscope^(a), and the cascade impactor. The greatest emphasis, by far, was on the cascade impactor. This device was developed in England for the work of the British Chemical Warfare Service at Porton. It was first described in the open literature by May (1945), but the Rochester people got details earlier through the Scientific Research and Development Section of the British Ministry of Supply and the U.S. Army Chemical Warfare Service.^(b)

(a) At this time, electron microscopes were scarce and were just entering the field. They were used later on in the MED studies at Rochester, but seem not to have entered as early as at Berkeley and Chicago.

(b) British-American collaboration in the field of atomic energy was smooth up to 1945. It was always good in aerosol research, at which the British were topnotch. In some other areas, such as sharing the ultimate secrets, they were not very smooth for a while (Hewlett and Duncan 1969), despite very significant early contributions by the British on the theoretical side.

Briefly, the device depends upon impingement of dust from jets of different sizes onto microscope slides, with each stage separating, to the extent possible, one range of particle sizes from another. The slides could then be photographed and the sizes counted, or the amount of material thereon simply weighed to give the proportion of the total dust on each stage, a great advantage in both time and convenience. There was usually some form of back-up filter to collect the ultrafines.

The uranium monograph gives full details of the original British cascade impactor and its use, including particle size distributions by optical measurement, by chemical analysis, calibration, design problems, etc., as well as a modified cascade impactor, which the Rochester people developed to overcome some of the problems of the British unit, such as durability in routine use and adaptability to uranium dusts. Also, the Rochester group found that size measurements and counts on the resin-coated impactor slides were not satisfactory. They developed a technique for selenium coating, in high vacuum, to obtain a high refractive index mounting. Details of this are given in chapter 10 of the uranium monograph.

The compendium from Rochester (uranium monograph) probably represents the most comprehensive description anywhere between two covers of the use of the cascade impactor for a specific set of dusts along with the full details for calibration and modification.^(a) It also is rich in details of the trials and tribulations as well as the successes of particle size determination during the years of World War II under the Manhattan District program. The identification and concentrated use of the cascade impactor were major contributions to the sophistication and usefulness of the Rochester inhalation experiments. The device has now come into quite general use, of course.

e. Relation of Particle Size to Toxicity

Earlier work, cited in part in the Rochester reports and in part in the general industrial hygiene literature, made clear that particle size could influence profoundly initial deposition in various segments of the respiratory tract, and to a lesser extent, the rates and degrees of lung clearance. At Rochester, LaBelle (1949, 1953) spearheaded an investigation of the influence of particle size on toxicity after deposition in the lungs. To do this he used carefully fractionated suspensions of UO_2 dust, which he administered by intratracheal instillation. Measurements were made of weight changes in the animals, of blood nonprotein nitrogen, kidney function, histological changes in lung and kidney, and the uranium content of selected tissues at one, two, and four weeks after administration. Maximum toxicologic response was seen at one week. The toxic effect varied inversely with the particle size. Particles of UO_2 smaller than $1\ \mu\text{m}$ were inherently more dangerous than larger particles. Also, transport out of the lungs and deposition in the femur increased with decreasing particle size. These seldom-quoted results are reproduced as figure 9.8.

(a) This device and its proper use became so much a part of the Rochester inhalation toxicology mystique that it was taught in-depth to health physics and industrial hygiene students in the postwar years. A seven-hour lecture hall session by one over-enthusiastic instructor not only turned some of the students off on aerosol techniques in general, but almost triggered a student revolt, which it became this author's duty to pacify. Dust can be dangerous in some unexpected ways!

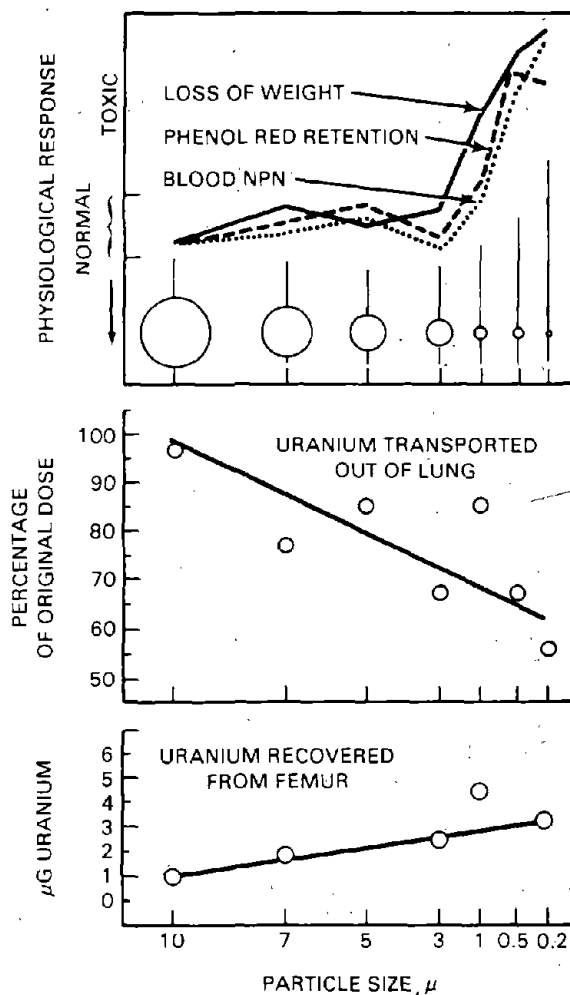


FIGURE 9.8. Changes in toxicologic responses and body transport of uranium in rats following intratracheal injection of 30 mg UO_2 /kg of body weight in graded particle sizes. Upper, retention of phenolsulfonphthalein dye (phenol red), body-weight changes, and changes in nonprotein nitrogen of blood; middle, transportation of uranium from lung; lower, deposition of uranium in femur. The circles in the upper figure give the relative size of the particles as if they were spherical. (Redrawn from Voegtlin and Hodge 1949, p. 510.)

An experiment with similar purpose, but using true inhalation, was performed near the end of the MED Project days. Preliminary results were published in the open literature by Wilson et al. (1948), and a fuller follow-up, done apparently partly postwar, was presented by most of the same authors several years later (Wilson, H. B. et al. 1955).^(a) This experiment used uranium triauroxide dust

(a) Further work was also described in the second part of the NNES compendium.

(U_3O_8) instead of uranium dioxide (UO_2). Since the aerosols were not monodisperse, only two "points" were available rather than the several seen in figure 9.8. The dispersions had mass median diameters of $0.5\ \mu\text{m}$ and $2.5\ \mu\text{m}$. Both rats and rabbits were used. The results were qualitatively similar to those of the intratracheal experiment. The particles with a mass median diameter of $0.5\ \mu\text{m}$ were much more toxic at the same concentration as evidenced by increased urinary protein, retardation of growth, and renal damage seen by histopathological examination. Deposition in lung, kidney, and femur were also greater with the smaller-particle-size aerosol, but subsequent redistribution was not affected. Surprisingly, the authors do not indicate whether or not they considered the difference in toxicity as fully explainable by the greater retention of the small sizes in important organs. Indirectly it can be concluded that they did not think so. The possibility that the smaller particles are more easily oxidized to higher oxides of uranium, which are more toxic, was speculated upon in some depth as a possible explanation for the greater toxicity of the small particles, i.e., it might have been due, in part, to a chemical difference. Indulgence in such possible explanations would not be expected if the difference in tissue concentrations explained the matter completely in the minds of the investigators. Incidentally, effects of the $2.5\text{-}\mu$ average mass median diameter were only marginal in the rabbit, and insignificant in the rat, while those of the $0.5\text{-}\mu$ range were significant in both species. The U_3O_8 dust concentration was $80\ \text{mg}/\text{m}^3$.

There were a few minor differences between the UO_2 intratracheal study and the U_3O_8 inhalation study. Nevertheless, the similarities were sufficient to indicate that *in this setting* the intratracheal method was a satisfactory substitute for inhalation once the differences in deposition in lung and upper respiratory passages had been accounted for.

This work on the effects of particle size per se on ultimate toxicity was unique in the MED work.

f. Biological Results in the Rochester Inhalation Studies with Uranium

The reader is reminded again that the biological endpoints of this uranium work were manifestations of chemical toxicity, primarily in the kidney, plus any systemic signs that proved useful. They are detailed extensively in the uranium monograph. They included periodic weight checks, chemical analyses of blood and urine, hematologic changes, and terminal gross pathology and histopathology. In addition, the uranium content of tissues was measured. Several physiologic tests, such as renal clearance in the dog, biopsy of renal tissue, liver function, etc. were applied selectively. Each compound, each exposure, and the peculiarities of each experiment are reported upon in depth. Each section is written by the investigator responsible for that segment of the work. Yet, because of the ubiquitous planning sessions and capable guidance, these disparate efforts form a coherent saga that needs only summarization in these pages.

Now let us have a broad summary of the results of this prodigious effort on biological effects. The basic biological changes were described in chapter 2. Summary results applicable specifically to acute inhalation exposure are shown immediately below; they will be followed by a summary of the effects of chronic exposure.

Table 9.5 gives a summary of acute toxic responses following daily inhalation of uranium dusts. The period of exposure was thirty days.

TABLE 9.5. Summary of Acute Toxic Response of Animals Following Repeated Daily Inhalation of Uranium Dusts

Approximate Concentration Level of Dust, mg/cu m	Response to	
	UF ₆ , UO ₂ F ₂ , UCl ₄ , UO ₂ (NO ₃) ₂ , 6H ₂ O	UF ₄ , high-grade ore, UO ₂
20	Generally fatal to most species; severe renal and frequently pulmonary damage	Occasionally fatal to some species; mostly moderate renal damage; severe renal damage in certain species only
2.5	Fatal to certain species; severe to moderate renal damage; occasional pulmonary damage	Nonfatal or rarely fatal; mild or no renal damage
0.2	Fatal to an occasional animal; slight renal damage in certain species	
0.05	Nonfatal; no histologic damage	

Source: Reset from Voegtlin and Hodge 1949, p. 688.

The soluble forms (left side of table) produced more effects at the high concentrations, and their range of effectiveness extended to much lower concentrations than that of the insoluble forms (right side of table).

Table 9.6 presents the "no-effect" levels in these same experiments. The presence of such a level presupposes that there is a threshold for response. In the radiation field, we have become habituated to thinking that no threshold exists for many of the critical biological effects. This is certainly not so true of chemical toxicology, and not true at all for the effects on the kidney, of primary interest in acute uranium poisoning. Thus a "no-effect" level has much more meaning for uranium than for strongly radioactive materials.

TABLE 9.6. Uranium-Dust Levels Producing Minimal or No Histologic Changes in the Kidney of the Dog

Dust	Lowest Level Showing Mild, Transitory Response, mg U/cu m		Highest Level Showing No Detectable Response, mg U/cu m	
UF ₆ , UO ₂ F ₂ , UCl ₄ , UO ₂ (NO ₃) ₂ , 6H ₂ O	0.2		0.05	
High-grade ore	1.0			
UF ₄	3.0		0.8	
UO ₂	10.0		2.0	

Source: Reset from Voegtlin and Hodge 1949, p. 688.

It will be noted again that the “insoluble” forms differ from the “soluble” forms, but along a more graded scale than the data in table 9.5 would predict. In the text, the authors state that “complete freedom from response upon repeated exposure to the soluble dusts is not attained until the level of 0.075 mg of uranium is reached. By contrast, the insoluble dusts produce no injurious effects at levels of from approximately ten-fold to thirty-fold higher concentrations” (Voegtlin and Hodge, 1949, p. 688).

A third measure is the toxic response score. The twelve uranium dusts were graded from UF_6 (most toxic) to U_3O_8 (least toxic) on a grid, shown in chapter 2 as figure 2.5.

A very full effort also went into *chronic* exposure experiments. While most of the actual exposures were done during the days of the Manhattan Project, the full-length published documents did not appear until 1953 (Voegtlin and Hodge, 1953). We will consider these chronic studies and their reports as part of the MED effort, even though final analyses and probably the bulk of the writing were under the Atomic Energy Commission (AEC) auspices.

It takes another 408 pages in the second pair of uranium volumes in the NNES series to present the chronic inhalation work and another 59 pages to present work using insufflation. The third and fourth parts of the uranium monograph, usually referred to as Part II,^(a) are devoted entirely to reporting all aspects of the chronic studies. There were eleven inhalation experiments of one-year duration and one two-year study. The primary reasons for this enormous extension of the work was establishment, as closely as possible, of a uranium dust concentration in air that would never produce even slight evidence of renal injury in an occasional animal. However, there were many secondary objectives, both scientific and practical. These can be seen best by excerpts from the introduction to the chapter on Chronic One-year Inhalation Studies:

Problems for the 1-year Study. The acute studies, however, left some important questions unanswered. Was apparent recovery complete, or would continued exposure produce a transition to a chronic form? Or would there be produced a series of acute attacks each followed by repair? Closely associated with the concept of chronic uranium toxicity is that of tolerance. Does the tolerance that was demonstrated to follow repair of acute renal injury in the short-term studies persist during continued exposure for 1 or 2 years at lower dust concentrations, or is acquired tolerance and chronic toxicity the same entity? Perhaps of greatest importance in long-term exposure is the storage of uranium in the body. Is it of such a degree as to constitute an injurious chemical accumulation or a possible radiation hazard, or does elimination keep pace with intake? At what sites of the body is deposition most marked; and how is this related to the solubility of the compound? There was obvious need for further, more prolonged studies. The chronic experiments described in this chapter were designed to fulfill this need.

(a). Aim of Chronic Studies. The objective of the chronic studies differed in one major aspect from that of the acute studies. Whereas emphasis in the short-term studies was placed on levels producing demonstrable injury, emphasis now was to be placed on the assignment of dust concentrations that would either

(a) All these “volumes” are considered as Volume I of Division VI but had to be bound in four parts, all labeled “VI-I.” Physically they are volumes, but they must be considered officially parts of one volume. One reason for this awkward arrangement is that the second phase covering the chronic work was not part of the original plan, and the uranium work, in toto, had been assigned as Volume I of Division VI (Rochester) of the NNES. Small asterisks on the cover tell readers which part they have in hand.

ensure a safe exposure for 1 year or produce minimal or borderline injury in the more susceptible members of a species. This objective was highly important since it would provide a measure of the required increase in concentration to produce minimal response over that required to produce none. The measure of this spread thus would provide information on the safety factor for each compound. To achieve this end it was obviously necessary to make at least two studies of each compound at different concentration levels. Moreover, because much time and expense went into such experiments, the number of studies had to be limited. The number of test compounds was restricted to five. Their choice was based upon three considerations: (1) the magnitude of the industrial exposure, (2) the representative nature of the compounds in regard to their physical and chemical characteristics, and (3) their relative potential contribution to fundamental toxicological knowledge. (From Voegtlin and Hodge, 1953, p. 1372)

In addition to meeting these practical objectives, many quite basic and universally applicable findings ensued as described in chapter 2.

The number of animal species used routinely was decreased to two, but the size of the experimental groups was increased. Much additional work on particle size was done. The single two-year study was operated by continuing exposure of animals from an insoluble dust exposure to a soluble compound at a higher level. There was an opportunity to perform serial pathology experiments so that the gradual development or the waxing and waning of lesions could be followed.

Even the essence of the results cannot be extracted in the space at our disposal. The reader will find the details clearly set out and identified with each experiment in the pages of the monograph. A few highlights can be set down here:

1. There was a distinct and typical response in the kidney to the one-year exposure that was qualitatively different from the thirty-day acute exposure. Whereas in the acute situation the animal either died or recovered fairly rapidly (and the kidney damage was repaired), in the chronic situation damage was relatively permanent. At high concentrations, it could progress beyond nephrosis to fibrosis of the kidney, but on the whole the changes were not markedly progressive.
2. At higher concentrations, the lung could be involved, sometimes to the extent of causing the animal's death.
3. The liver was sometimes involved, but never critically, at even the highest levels.
4. There was no evidence of radiation damage.
5. No neoplastic changes or frank cancer were reported. (Little is said about cancer in this work, but it is presumed that the pathologists were alert to its possible occurrence.) This may mean that one year is still much too short a time to develop cancer from natural uranium exposures (see chapter 2).
6. There is a definite change from acute to chronic injury, but the characteristics of acute injury can reappear. Also, acute injury is a necessary prerequisite for the development of the chronic type injury characteristically seen in the kidney tubules. Thus the "chronic injury" may represent incomplete or improper repair of an acute injury. As implied above, and unlike many types of long-term injury, the uranium lesions did not usually become progressively worse. In fact, even the chronic type injury showed reversal and repair if exposure ceased. *This has important implications for the*

epidemiology of uranium exposures in man and the validity of claims for compensation for exposures long since discontinued.

7. On the basis of over one-half million observations, it had to be concluded that functional changes such as blood or urine biochemistry were more transitory than the morphological changes. They were not nearly as reliable as the information from kidney biopsy or serial histopathologic examination of tissues and were not reliable indices of underlying biological damage.
8. Hematological changes were likewise not a good measure of the presence or absence or degree of chronic injury. While there were changes, they were more transient and more variable than the kidney lesions.
9. Weight change correlated moderately well with development of early kidney damage, but, at later times, weight response was not a reliable measure of the degree or progress of chronic toxicity.

All of these conclusions, even though broadly and qualitatively stated, bear on the interpretation of chronic exposure of man to natural uranium. We reviewed some of the extant dilemmas in chapter 2. We will address the issue further in chapter 16. Suffice it for now to point out the marked difference in progression of the lesions and in the ability of the organism to handle moderately toxic levels of uranium compared to the more radioactive materials such as plutonium and other transuranics, polonium, and the fission products.

g. Deposition and Retention of Inhaled Uranium (Chronic Exposures)

We reviewed in chapter 2 the fact that uranium is a bone-seeking element and the general features of its metabolism; here we will look briefly at its behavior on and after inhalation. We will adopt the conventions of modern inhalation toxicology and use "deposition" to refer primarily to the amount of inhaled material deposited in the respiratory tract and "retention" for the behavior after deposition. For what was frequently called deposition when absorbed material reaches an organ, other than lung, we will substitute the word "uptake."

The behavior after acute exposures has already been reviewed briefly. We will concentrate here on the most prominent features from the chronic inhalation studies of the MED days.

1. Only a few sites are involved in *deposition* of uranium dusts, viz., lung and its draining lymph nodes. Transfer occurs almost entirely to bone (including the tooth structures) and the kidney, if the salt is relatively soluble.
2. Uptake is primarily in kidney, especially for soluble salts, but kidney does not accumulate uranium. It soon reaches an equilibrium concentration where uptake and loss balance.
3. Bone is the only tissue that accumulates uranium after exposure by inhalation of soluble salts. The accumulation is modified by exposure level. Below 0.25 mg uranium/m³ exposure concentration, there is no appreciable accumulation in bone or any other tissue over one or even two years.
4. Naturally, the very insoluble forms (UO₂) remain fixed in lung and accessory lymph nodes for considerable periods. Amounts as high as 7,000 µg/g were found in lymph nodes, 1,500 µg/g in lung at the end of one year of exposure to UO₂ at 10 mg/m³. The amount in bone, in the same experiment, was about 5 to 10 µg/g and in kidney 1 to 5 µg/g. Thus, the lung and lymph nodes might be considered vulnerable to the insoluble dusts of uranium,

but their sensitivity is far less than that of the kidney (see chapter 2). Also, binding seems not to be so tight that the uranium cannot leave once exposure ceases.

5. Retention of uranium in all tissues but bone is not as avid as we have seen for materials such as plutonium.
6. Of particular interest is the fact that insoluble uranium deposited during a one-year exposure continued to leave the lung despite the fact that a second year of exposure was under way, this time to a soluble compound.

Extensive graphic and tabular summaries are contained in the uranium monograph.

h. A Special Deposition Experiment

A central and difficult problem in all inhalation experiments is determination of how much of an inhaled material is deposited on a breath-by-breath basis. Most estimates rely on immediate sacrifice of a few animals and comparing the amount found in these animals with the amount inhaled as calculated from the chamber concentration and the estimated ventilation rate of the animal's lungs. As part of the Rochester uranium studies, toward the end of the Manhattan Project days, LaBelle et al. (1953) devised an elaborate, and for its time, sophisticated apparatus to determine what fraction of the uranium in a single inhalation was retained. The apparatus was based on a method developed by Drinker, Thomson, and Finn (1928), which was in turn developed from a design by Baumberger in 1923. A diagram of the general setup is given in figure 9.9A, and the special facepiece is shown in figure 9.9B.

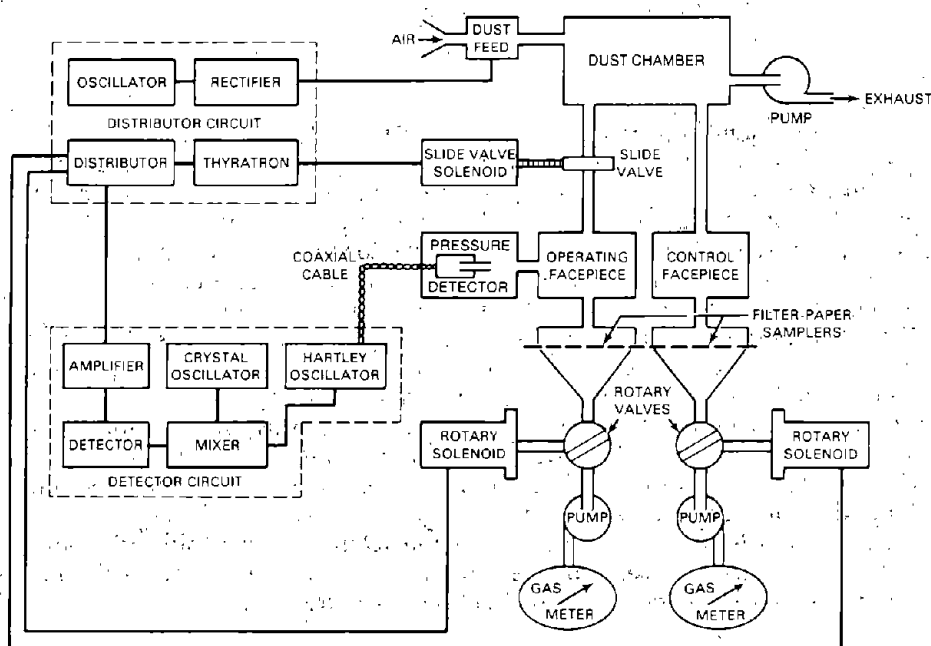


FIGURE 9.9A. General layout of apparatus for retention experiment. (Redrawn from Voegtlin and Hodge 1953; p. 1980.)

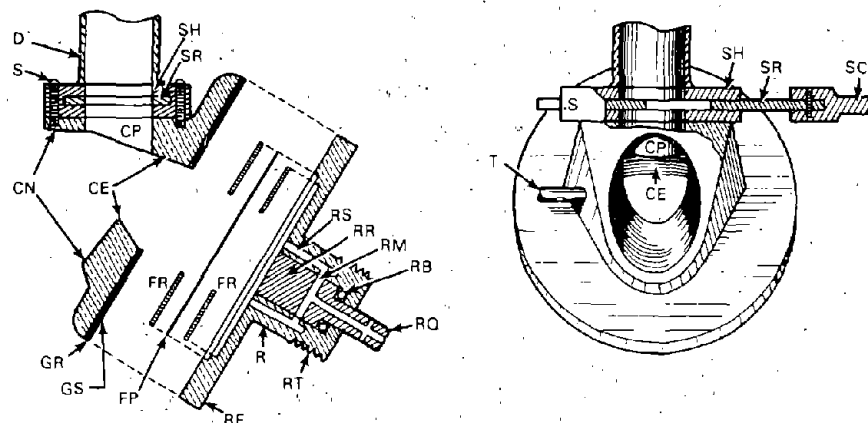


FIGURE 9.9B. Diagram of facepiece and valve assembly. CN, nasal cone in which rabbit's head is inserted; CP, opening through which dusty air enters; CE, space into which rabbit exhales; D, duct leading to dust chamber; FP, filter paper on which sample is collected; FR, filter-paper retainer rings; GR, rubber gasket; GS, raised ring to provide seal; R, rotary-valve assembly; RF, flange; RR, rotating plug; RM, T-shaped duct through plug; RS, ducts in valve housing; RQ, hollow quill through which air leaves valve; RB, ball bearing carrying thrust of valve plug; RT, thread to fit rotary-solenoid housing; S, slide valve; SH, slide housing; SR, slide; SC, link to transverse solenoid; T, tap for pressure detector. (Redrawn from Voegtlin and Hodge 1953, p. 1685.)

By means of sensitive circuitry, which activated solenoids attached to slide valves, the very small pressure changes between the end of inspiration and beginning of expiration would cut off the operating facepiece from the chamber, allow collection of expired air, and measurement of its uranium content. The control facepiece (figure 9.9A) allowed collection and measurement of the inhaled air through a path as similar as possible to that entering the operating facepiece. The difference between these was the amount deposited.

The results, using uranium dioxide, indicated that absolute deposition varied as the $3/2$ power of the concentration. Thus, the percentage of deposition increased with concentration and approached 100% at the highest concentrations (range was 10 to 250 mg/m³). Two particle sizes (distribution not given) were used, 0.5 μ and 1.0 μ . There was little difference between them.^(a)

The deposition was directly proportional to the volume of air breathed and independent of the rate of breathing.

Variations in respiratory volume can be equivalent to a five-fold variation in effective concentration. Variation between animals was somewhat less important (equivalent to a factor of two in effective concentration).

(a) A 0.5- μ particle of uranium dioxide is aerodynamically equivalent to a much larger particle of a lighter dust. Thus, the efficiency of impaction of even the smaller particles of uranium in the respiratory tract would be quite high.

There is little doubt that these measurements, done sometime before publication in the monograph, influenced the development of so-called lung models used in establishing maximum allowable concentrations. These will be examined in chapter 16. Hodge (1980) recalled that one of the prime motives for work of this type in the Rochester program was the development of respiratory-tract models. Perhaps these findings were involved in some of the first models developed at the Chalk River Conference in 1949 (chapters 8 and 16).^(a)

i. More Particle Size Versus Toxicity

To cap off this volume-sized report of the Rochester experiments on chronic toxicity of uranium, there is a further detailed report on the effect of particle size on toxicity (LaBelle 1953). Both inhalation and intratracheal instillation of rats and rabbits were used.

The earlier conclusion that smaller particles were more toxic was strengthened. Further, it appeared that $1\ \mu$ was sort of a breaking point. Particles smaller than $1\ \mu$ were progressively more active, and there was no indication that a limit had been reached at the smallest size tested, viz., $0.35\ \mu$. There was not as much change above $1\ \mu$ as below.

This time the investigators really searched for explanations. They found that the variation in quantity of uranium gaining access to the systemic circulation and toxicity correlated well. However, the amount leaving the lung was not a good measure of the quantity entering the systemic circulation, a surprise to the investigators. Appreciable fractions of the uranium dioxide were leaving the lung by some route that did not involve the circulating blood. Furthermore, the removal by this route was such that the *larger* particle sizes were removed more efficiently. We will need to reconsider this dilemma when we review the post-war inhalation toxicology work.

j. Comment

There is no doubt that the strong emphasis on inhalation work in the Rochester program under the Manhattan Project, and the prodigious proportions of the effort, brought inhalation toxicology solidly into atomic energy research. As we will see in the next sections, the momentum carried into postwar research unabated.

Harold Hodge has commented (1980) on the inordinate amount of work involved in many of the inhalation experiments to get only a few points on a graph or figures in a table.^(b) An equivalent effort in many other fields would yield tangible results in much less time. It is fitting, therefore, that the Rochester effort could produce new centers to help carry on the work begun under the pressures of wartime research, as we will see in the following sections.

(a) Like most such conferences, the origin of the values used is not recorded, and is known only to those present. Very recently, Taylor has brought together all of the extant minutes and notes from the Tri-Partite Conferences (Taylor 1984). This yeoman service finally brings at least the substance of the heretofore "private" conferences into public view.

(b) While the same is true of all truly long-term experiments, the inhalation program, with almost daily exposures continuing over months, even years, undoubtedly heads the list for sheer drudgery.

III. The Postwar Years Begin

In striking contrast to the situation during the war years, the new work has been very adequately presented and reviewed. Management had compelling practical reasons for supporting the research and being sure its results were readily available. There was considerable interdisciplinary exchange of interests and ideas between the aerosol scientists and those in radioactive inhalation toxicology (pulmonary radiotoxicology)^(a) on the one hand; and between the people interested in radioactivity and those in conventional industrial hygiene on the other. In some installations, all three types worked closely together. The literature of the field is fairly readily accessible, but it is voluminous. In this section, we will review the major programs, contributions from less major programs, and some areas requiring special attention.

A. Continuing Work at Former Manhattan Project Laboratories

At the termination of World War II, Chicago and Berkeley (i.e., Argonne National Laboratory and the University of California Radiation Laboratory [UCRL]) eschewed almost completely further experimental work in the radioactive inhalation field except some follow-up studies. Of the three prime movers of the war years, only Rochester continued as a center for inhalation toxicology.

Some of the early postwar quarterly reports from Berkeley discussed results of autoradiographic work done to follow up on the aerosol exposures done during the war. Since they were dealing with long-lived alpha emitters, they could go back to some of the tissue blocks prepared in the 1944–1946 work and do new autoradiographic exposures with improved techniques. Results were reported by Asling and Thilo in two UCRL reports (1951, 1952). They were able to emphasize histologic localization of deposition sites and the movement of materials as a function of time after inhalation. They observed not only the evidence of activity concentrated in macrophages and along alveolar walls, but also rather generalized single tracks throughout the tissue. They also noted macrophages in process of apparently disintegrating and releasing their activity. All of these have been seen in other postwar experiments, but these go back the furthest. Examples are shown in figure 9.10A and B.

At Chicago, an extension of the MED work is found in pathology reports by Lisco and Finkel (1949) and by Lisco (1959). Both are firsts. The report by Lisco and Finkel (an abstract) concerns pathology following inhalation of radioactive cerium. It constitutes, it appears, the first report of a lung tumor produced experimentally by the beta particles from an inhaled radioisotope. The 1959 paper by Lisco reports that 50% to 100% of rats surviving 250 days after receiving a $^{239}\text{PuO}_2$ smoke developed epidermoid carcinoma. (The dose was 0.2 to 1.0 μCi .) While not the first report of the production of lung cancer by plutonium, according to Bair (1960), it is the first report of carcinoma after inhalation of a plutonium aerosol. Both reports are cryptic on experimental detail, since

(a) This term was coined by H. D. Bruner for a paper given at a symposium at Sandia Laboratory in Albuquerque in 1967 (Bruner 1967). Dr. Bruner played a key role in the development of the AEC inhalation program. Despite the appropriateness of the term, it seems not to have come into general use. Perhaps too many people were already in the field by 1967 and were calling themselves something else. We will use it here as seems appropriate.

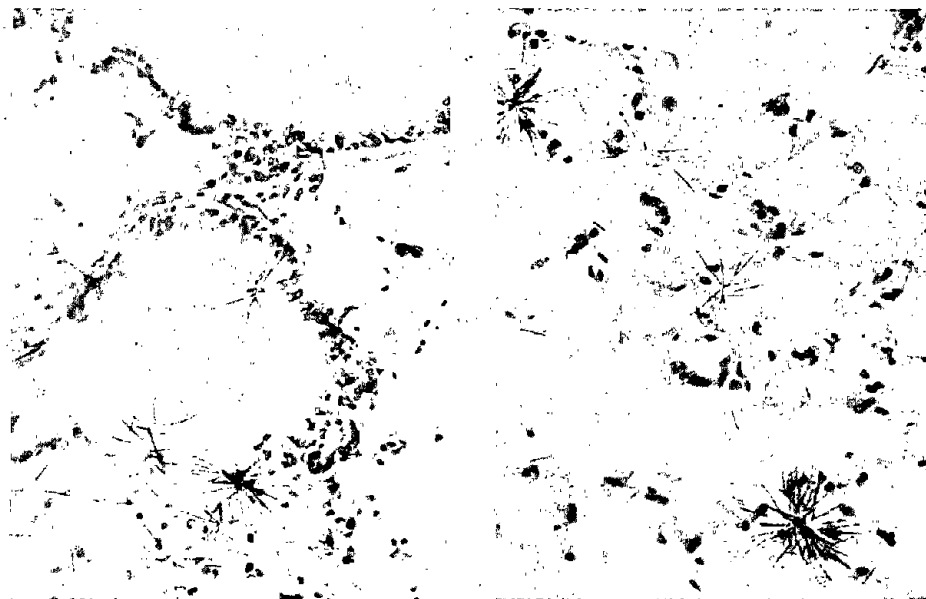


FIGURE 9.10A. Autoradiographic evidence of plutonium oxide within pulmonary macrophages five days after exposure to a plutonium smoke. (Photo courtesy of Dr. Patricia Durbin.)

FIGURE 9.10B. Evidence of aggregated plutonium in lung tissue five days after exposure to a plutonium smoke. (Asling and Thilo 1952; photo courtesy of Dr. Patricia Durbin.)

these reports represent the results of pathological examination of materials from the animals exposed during the war by Abrams et al.^(a)

The work at Rochester in the postwar years can be considered in two parts, that which was a direct extension of the wartime effort and work that was essentially new.

The *direct extension* of the wartime effort into the postwar years was the eleven-year-long uranium experiment, which we reviewed in chapter 2. That experiment assumed heroic proportions. Among other things, it showed that, with sufficient perseverance, radiation effects can be brought about by natural uranium.

A corollary extension of the wartime work was that the Rochester Project became a center for training both for regular academic students and for shorter-term industrial trainees in pulmonary radiotoxicology. As a result, many of the laboratories that developed and came into flower in the postwar years were manned, in part, by people who had either worked in the Rochester program or received academic training there in the early postwar years. Several became laboratory directors or senior scientists in the new programs we will consider presently.

(a) It is rumored that there may be still other left-over material, or was until recently, awaiting the needed analysis by pathologists. Fortunately, such material has a long shelf-life; but the records sometimes become meaningless as the keys to animal codes, etc., get lost, or their interpretation hazy.

A few photographs taken of some of the early postwar classes at work in industrial hygiene and aerosol science at Rochester are reproduced as figure 9.11A, B, and C. More details concerning the Rochester research programs are presented in later sections.

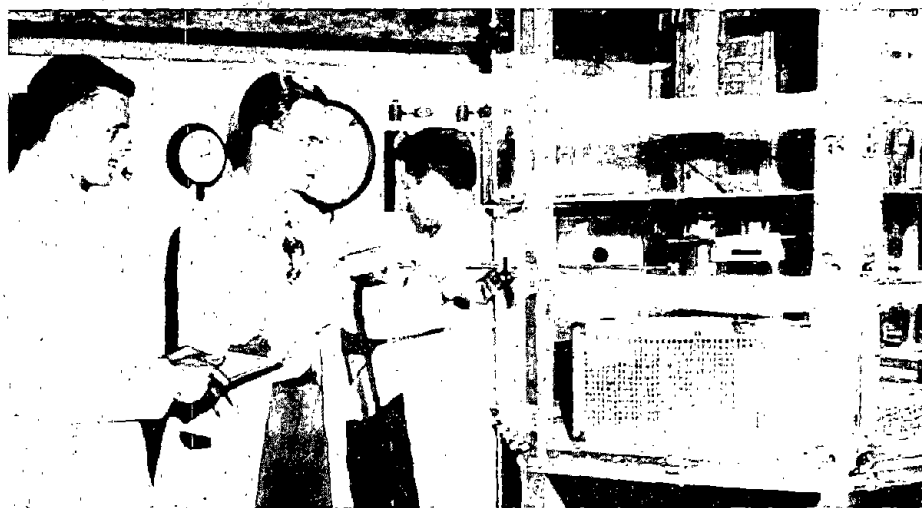


FIGURE 9.11A. Students at the University of Rochester in early postwar years gaining experience in pulmonary radiotoxicology. Taking air samples from model exposure chamber left to right are: W. J. Bair, now manager of the Life Sciences Center, Battelle, Pacific Northwest Laboratories; George Angleton for many years at Colorado State University; and Robert Barker, with the Nuclear Regulatory Commission for many years. (Photo courtesy of the University of Rochester.)



FIGURE 9.11B. View of control panel and at left the "Pickle Jar" inhalation chamber and students in industrial hygiene course. (Photo courtesy of the University of Rochester.)



FIGURE 9.11C. Several "Pickle Jar" inhalation chambers for student use including accessory pumps and aerosol generators and more students in the industrial hygiene course. (Photo courtesy of the University of Rochester.)

B. Aerosol Science

1. Development of Liaison

The struggles the radioactive inhalation people had during the war in preparing and measuring aerosols were not unique. They were only exacerbated by the technical problems of handling radioactivity. As we remarked earlier, aerosol problems touch upon a great many aspects of technology and research. These fields grew tremendously during and soon after the war, and so did aerosol science. With the lifting of security restrictions, communications took on new dimensions, and the close interrelations between the problems of coal mines, dusty trades, infectious diseases, air pollution, and the radioactive inhalation field were underscored. Particularly industrial hygiene and pulmonary radiotoxicology joined hands.

The field was blessed by the timely appearance and brisk use of many monograph-type books. There was a new edition of the classic book first written in 1936 by Drinker and Hatch entitled *Industrial Dust* (Drinker and Hatch 1954). Soon came a corresponding classic from the east side of the Atlantic, *Particulate Clouds: Dusts, Smokes and Mists*, by H. L. Green and W. R. Lane (Green and Lane 1957). Along with these are important later comers, such as *Particle Size, Theory and Industrial Applications* (Cadle 1965), and *Particle Size Analysis in Industrial Hygiene* (Silverman, Billings, and First 1971). Also in 1971, Mercer, Morrow, and Stöber edited a volume on *Assessment of Airborne Particles* (1972). A very useful volume in the AIHA/AEC Monograph Series entitled *Aerosol Technology and Hazard Evaluation* was produced by Mercer in 1973 (Mercer 1973). Finally, a very fundamental volume on aerosol behavior was prepared by

S. K. Friedlander (Friedlander 1977). This last is a text prepared by Dr. Friedlander from notes for his advanced undergraduate-graduate student course at the California Institute of Technology. These books provide ample general reference material. Perusal of these should satisfy any reader that the physicochemical aspects of the field have been well quantified; that some reasonably reliable laws exist; and also that the biological side is more difficult, more unpredictable, and less developed.

In view of the pressing practical problems in industry, it is not surprising that the applied side was especially active. Very soon after the war, the U.S. OSRD published a *Handbook on Aerosols*. Over twenty-five years later, this very useful handbook was updated and revised by the U.S. Energy Research and Development Administration (ERDA) (Dennis 1976). It is full of tabular information important to anyone with responsibilities for air contamination, measurement and control. In addition, because of the special needs of the AEC contractors to remove the last vestige of toxic particles from waste gas streams, and for their control and measurement, the commission sponsored periodic "Air Cleaning Conferences." The first seventeen of these have been tabulated recently by Burchsted (1981).^(a) Given below is an excerpt from this publication that gives the site and year, and also the publication number for the several conferences.

AEC/ERDA/DOE Nuclear Air Cleaning
Conference Document Numbers

Conference Number	Conference Year	Conference Location	Document Number
1	1951	Boston	No Proceedings
2	1952	Ames	WASH-149
3	1953	Los Alamos	WASH-170
4	1955	Argonne	TID-7513
5	1957	Boston	TID-7551
6	1959	Idaho Falls	TID-7593
7	1961	Brookhaven	TID-7627
8	1963	Oak Ridge	TID-7677
9	1966	Boston	CONF-660904
10	1968	New York	CONF-680821
IAEA	1968	New York	CONF-680811 ^(b)
11	1970	Hanford	CONF-700816
12	1972	Oak Ridge	CONF-720823
13	1974	San Francisco	CONF-740807
14	1976	Sun Valley	CONF-760822
15	1978	Boston	CONF-780819
16	1980	San Diego	CONF-801038

The number of aerosol scientists with leanings toward applications in the biological sciences and in industrial hygiene was never large. Even fewer gained expertise also in the field of radioactivity or the handling of radioisotopes. During the war, as we saw, the people who needed the results worked in collaborative groups on the techniques of exposure and measurement. In the postwar

(a) The eighteenth conference was expected to be held in August 1982 in Denver.

(b) Available from the International Atomic Energy Agency (IAEA) as STI-PUB-195.

period, there gradually developed a tendency to have either specific aerosol science sections around the major inhalation projects or to have some experts in aerosol science easily available to the bioscience groups.

The idea of having a specific aerosol section was probably first implemented at Rochester. This became a natural milieu by the presence of a graduate program and academic research opportunities. The long-term uranium experiment (chapter 2) was going ahead, more or less on the old basis, aided greatly by the use of the Wright dust feed (Wright 1950), another idea introduced from England.^(a) Some of the wartime people with aerosol experience were still available (Charles LaBelle, Sidney Laskin, Kenneth Lauterbach, and Robert Wilson, among others), but some were beginning either to scatter to industry, to other universities, or to other duties at Rochester. At about this time, a Ph.D. student in pharmacology, Thomas T. Mercer, who had a knack for quantitative science and a good pair of hands for building equipment, decided he preferred what he had seen in the aerosol work to conventional pharmacology. Toward the end of Mercer's Ph.D. journey, one of the central figures of British Aerosol Science, Dr. C. N. Davies, visited Rochester, gave some seminars, and he and Mercer met. In due course, arrangements were made for Mercer to serve a postdoctoral period with Davies, whose primary work concerned coal dusts and the work of the British Coal Board. On completion, Mercer returned to Rochester to organize one of the first Aerosol Science sections built around a radioactive inhalation program.^(b)

The Aerosol Section, as organized, provides advice to those doing inhalation experiments, but is far from a service organization. Indeed, their focus is on fundamental aspects of the science.^(c) This has led to several modifications of technique in programs at Rochester and elsewhere and attacks on basic problems, such as the role of electrical charge phenomena—especially important, and troublesome—in work with radioactive aerosols. Some of this work will come to our attention as we review the postwar inhalation studies, but for most of it the reader is referred to the literature already cited, and papers in the several aerosol symposia.

Another Rochester Ph.D. student, Otto Raabe, had his interest in aerosol science kindled while in a biophysics program. In due course, he went to the Lovelace Fission Product Inhalation Laboratory to fill the job which Mercer had vacated. There he remained until recently when he moved to the University of California at Davis. He did much work on the *in vitro* solubility and dissolution of particles in simulants of lung fluid (see section IV B). During the interim, between Mercer's departure and Raabe's coming to Lovelace, Robert G. Thomas, a much earlier Rochester graduate with broad interests in the entire

(a) The cascade impactor was the first, as we saw earlier.

(b) The plan nearly came to grief when Mercer, a native of the Pacific Northwest, was enticed to the University of Washington for a while and then went to be the aerosol anchorman at the new Fission Product Inhalation Laboratory at the Lovelace Foundation. However, he eventually returned to Rochester and headed the Aerosol Section for the balance of the period of interest in this book.

(c) For reasons that are not really clear, the excellence of this aerosol group seems to have been appreciated more abroad than in the United States. There have been numerous visiting scientists from Europe in the laboratory from postdoctoral fellowships up to faculty appointments. Several have returned to senior posts in Europe; a few have stayed.

field of pulmonary radiotoxicology, devised many experiments involving aerosol exposure techniques and the importance of particle size in toxicity.

Yet another product of the Rochester program was Robert Phalen, who now presides over important and complex exposure units in the Department of Community and Environmental Medicine at the University of California at Irvine. He also conducts basic aerosol research in the field of air pollution.

The Lovelace aerosol group initially felt the loss of Mercer very keenly (McClellan 1981). The help from Thomas's and Raabe's coming helped at a critical time. They developed a strong and active aerosol group under the supervision of George Kanapilly.^(a) By September 1981, the Aerosol Science group listed nineteen personnel, including six with Ph.D. degrees and one with a Sc.D. Some of these take part, of course, in the development of facilities for inhalation exposures. There is also a section called "Exposure Operations Section" under the Aerosol Science group. This group in toto may be one of the most extensive flowerings of the formally organized Aerosol Science group within an inhalation toxicology program. It has been especially appropriate to this laboratory as it expanded beyond radioactive inhalation problems to very general inhalation toxicology.

At Hanford, the development of aerosol science took a different course, especially in the first two decades after World War II. Radioactive inhalation work began in about the mid-1950s.^(b) There was already a strong program in atmospheric science in another part of the operation under James Fuquay, which included Lyle Schwendiman and Jofu Mishima. For many years, the principal investigator (W. J. Bair, whom we met in chapter 8) and his closest associates (D. H. Willard and L. A. Temple, among others), with help from plant-wide liaisons, devised exposure chambers, aerosol generators, measuring systems, etc. Like many others, they were patterned after existing models in principle but soon assumed special characteristics for the purposes at hand. During the ensuing years, Bair and his group developed a number of important and unique aerosol administration devices, including face masks for dogs, a device by which beagles could inhale radioactive dust as well as smoke cigarettes, and a wide variety of exposure chambers for different purposes. Bruce Stuart, who received his training at Rochester, but in another field, was especially active in some of these developments. Occasionally, someone from the sister department, the section on Radiological Development and Calibrations of the Radiation Protection Operation, would join forces with the biologists sufficiently to become a coauthor (e.g., Swinth) or to prepare independent publications concerning aerosol problems (e.g., Healy, Roesch, Anderson).

On the occasion of delivering a series of lectures in Japan in 1969, Bair (1970) reviewed and pictured the many types of exposure rigs they had devised.

By the 1970s, the annual reports from what had now become the Biology Department of PNL, which is operated by Battelle Memorial Institute, cited work in a section termed, "Development of Aerosol Exposure and Analytical Techniques" with W. C. Cannon listed as "Person in Charge." D. K. Craig was part of this group and later was responsible for Battelle's earliest approach to a specific aerosol section. Craig received a Ph.D. at Rochester with a thesis in

(a) They do train bioaerosol scientists at places other than Rochester! Kanapilly was trained at Wayne State University.

(b) The development of the Hanford/Pacific Northwest Laboratory (PNL) inhalation program will be reviewed in section IV A.

"pure" aerosol science (see Craig 1962). He was originally a research officer for the South African Atomic Energy Board, but elected to return to the United States a few years after completion of his Ph.D. Fredrick Cross, still another Rochester graduate, whom we met in connection with radon problems in chapter 3, was close by in the sister group. It might be said that this organization was a counterpart of the specified aerosol sections at Lovelace and Rochester. Certainly they engaged in fundamental aerosol research as well as taking part in the inhalation toxicology program. However, it seems not to have been quite so formalized as some of the other groups. After Craig left to take up duties at Headquarters in Washington, Owen R. Moss, another University of Rochester graduate, joined Cannon and others in the group. Moss had had considerable experience in aerosol work.

At Los Alamos, the Industrial Hygiene group under Harry Schulte represented the core of aerosol science. Only for some specific problems (see section V A, and work around the field tests) did the biology and medicine groups get very much involved with aerosol research.

In New York at the Health and Safety Laboratory (HASL), which operated under AEC and ERDA, and now as the Environmental Measurements Laboratory under the Department of Energy (DOE), we see yet another way in which aerosol science was folded into pulmonary radiotoxicology. This laboratory started as part of the New York Operations Office and had special responsibilities for uranium dust problems, even in the Manhattan Project days. Over the years, it became as much involved with environmental as with occupational problems. It was a center for measurements of fallout throughout and after both the Continental and Pacific atmospheric testing programs, as we will see in some detail in chapter 12. We have already seen (chapter 3) something of its involvement in radon measurements and the uranium miner problems. The laboratory devoted much of its effort to the development of methods and instrumentation for the assessment of levels and hazard and has provided definitive documents on natural background radiation. In a sense, the Health and Safety Laboratory provided a base in aerosol science as well as in other pertinent methodological and instrumental areas to the whole of AEC and its successor agencies much as the specific sections within laboratories served specific laboratory programs.^(a)

The Institute of Environmental Medicine at New York University (NYU) has had a strong general aerosol science component in its operations throughout its existence. With this we associate names like Merrill Eisenbud, who came to NYU from the precursor of HASL with much experience in the problems of inhalation of uranium and beryllium dusts; McD. Edward Wrenn, a home-grown product; Sidney Laskin, who went to NYU from Rochester; Norton Nelson, the Institute's very broad-gauged director; Bernard Altshuler, an old pro for aerosols and modeling; and, in later years, Naomi Harley and B. S. Pasternak and others whose work we have seen or will soon meet. This laboratory, much like Battelle's, operated with most of the aerosol experts as part of the team for a given experiment, and no separate aerosol section.

Many other laboratories, e.g., in the Graduate School of Public Health at the University of Pittsburgh, the U.S. Public Health Service Laboratories in Cincinnati, and others were engaged in aerosol science activities; a few of which

(a) I am greatly indebted to Dr. John H. Harley, recently retired director of the laboratory, for a capsule history and selected publications pertinent to radiation toxicology (Harley 1981). We will quote these in proper context.

e.g., the work of Cember at Pittsburgh) were oriented toward radioactive inhalation problems. We will review these later. The reader can find their more general contributions in some of the monographs mentioned earlier, and in the journal literature of industrial hygiene and occupational medicine.

2. Generalization of Results in Aerosol Science

From our review of pulmonary radiotoxicology, a few items of essentially universal applicability from the work in aerosol science and related areas should be summarized.

a. Role of Particle Size in Deposition

The advances in methodology in the postwar years permitted determination of pulmonary deposition over a very wide range of particle sizes. The region of ultra-small particles is only now being addressed by Stahlhofen and colleagues. From essentially no deposition above about $20\ \mu$ activity median aerodynamic diameter (AMAD), the pulmonary deposition reaches a maximum at between $1\ \mu$ and $2\ \mu$, decreases to a minimum in the region around $0.5\ \mu$, and then appears to rise slowly in the region where Brownian motion is important.

The above is a generalization for alveolar deposition. Deposition in the nasopharyngeal region is skewed sharply toward the larger sizes. The tracheo-bronchial region shows much less deposition than either nasopharyngeal or pulmonary regions, but there is a distinct rise in the deposition fraction below $0.05\ \mu$ mass median diameter (MMD). These relationships apply equally well to nonradioactive or to radioactive aerosols.

Detailed discussions and diagrams can be found in the report of the Task Group on Lung Dynamics of the International Commission on Radiological Protection (TGLD 1966), reviews by Stuart (1973, 1976), ICRP 1980, and the monographs already cited. A particularly clear exposition of the several physical forces (gravitational settling, inertial impaction, Brownian motion, coagulation, electrical charge, condensation, thermal effects, and concentration) can be found in a review by Morrow (1960). Actual experiments are legion. We will cite two: an early set by Brown et al. (1950) at Pittsburgh and the Mellon Institute and one in man by Morrow et al. (1958) at Rochester.

A summary of the respiratory tract deposition models in animals and man was prepared recently by the Lovelace group (Yeh 1980) and is being examined in detail by both the ICRP and the National Council on Radiation Protection and Measurements (NCRP).

b. Practices

The above generalizations did much to reorient operations in practical air sampling. The importance of selective size sampling, especially to distinguish respirable dust, was appreciated. Many devices for routine sampling that could make that distinction were developed. The philosophy behind this is addressed in some depth by Morrow (1964).

c. Role of Physiological Factors in Deposition

While the biological factors were sometimes a source of irritation to the aerosol scientists, who were usually physical-science oriented, they were inevitably present in the experiments. Parameters like tidal volume, respiratory rate, ventilation rate as influenced by the work rate of the subject, had to be separated out and their importance evaluated. It turned out that ventilation rate and tidal

volume could easily have as much influence on deposition as particle size. Thus, the deposition curves form an envelope when plotted against particle size—the envelope reflecting the influence of physiological factors, as well as the range of variability.

d. Retention and Clearance

In our review of the wartime work, we saw the first indication that particle size could affect clearance and ultimate toxicity as well as deposition. In the postwar work, many other parameters and processes entered the picture. The basic findings of the war years were not controverted. However, the new work showed that the picture was not as simple as the early Rochester work predicted. For example, Boecker (1962) found that thorium chloride remained in the lung longer the larger the particle size. (The difference could amount to a factor of three.) Similar results were reported from Hanford with plutonium. However, retention in the *whole body* (using whole-body counting methods) showed just the opposite relation. Part of this discrepancy rests on amounts cleared from the lung early-on versus later. A thorough treatment of the influence of aerosol properties on distribution, retention, and excretion is given in papers by Thomas (1964a,b; Thomas et al. 1973) using aerosols of antimony, plutonium, polonium, niobium, uranium, and thorium. Particle size has a marked influence on subsequent behavior, but it can be overshadowed by differences in chemical form.

Interestingly, and despite the intrusion of many other parameters, Parsont, Holley, and Burnett (1972) return, in modern modeling garb, to the earlier work on particle size and point out how the lung dose decreases for small particles ($\leq 1 \mu\text{m}$), while the dose to other internal organs increases correspondingly because of more rapid removal of the smaller particles from lung to other tissues. They point out that this may change the critical organ from lung to some other organ or tissue (e.g., liver or kidney) and admonish the ICRP to incorporate these considerations in the official lung model.^(a)

e. Mechanisms of Lung Clearance

The work on mechanisms of lung clearance is more in the domain of biomedical scientists than of aerosol scientists. However, the teamwork approach soon involved the latter in this largely biological and biochemical enterprise. A review paper by L. J. Casarett (1960) sets forth the primary processes, i.e., movement by ciliated epithelium, phagocytosis, lymphatic absorption, and solubilization.^(b) The aerosol people got especially involved in the latter.

Rather sophisticated kinetic analyses have been made of the clearance of inhaled particles (Morrow 1977). The presence of many patterns has become obvious from the prodigious assembly of experiments on plutonium and related actinides gathered and presented by an ICRP task group chaired by W. J. Bair (ICRP 1980) and from the summary in the same volume for experiments on beta-gamma emitters. These do not always yield to mechanistic analysis, but approximations as to what is going on in vivo are reasonably satisfying.

f. Special Considerations for Radioactive Aerosols

The work in aerosol science found many ways that the presence of radioactivity modifies some of the generalizations. For example, the electrical-charge

(a) The model does provide for calculations at other than the standard particle size.

(b) We would now include diapedesis via lymphocytes or even of naked particles through the alveolar wall in this listing.

characteristics of the radioactive aerosol may differ from the nonradioactive one simply because of the ionizations produced by the decaying atoms.

A most important consideration is the relation between mass and toxicity. For most chemical aerosols, the toxicity is related to mass unless surface area characteristics play a definitive role. Thus, the curves for deposition as a function of particle size reflect ultimate toxicity so long as we are not dealing with vector aerosols.^(a)

The aerosols of radioactive materials are almost always of the vector type, i.e., the activity becomes attached to particles of nonradioactive dust. As Stannard pointed out (1959), quoting work by Mercer and Wilkening, radioactivity does not necessarily attach to the vector aerosol particles in proportion to their mass. In fact, both natural radioactivity and artificially produced radioactive aerosols may have a disproportionate amount of their activity associated with the smaller particle sizes. Thus, it might be very wrong to predict hazard from the behavior of the vector. The maximum activity may occur where the mass deposition is quite low.

To avoid this potentially dangerous mistake, it has become customary to characterize radioactive aerosols in terms of activity, i.e., the AMAD. This is especially important for aerosols of substances of high specific activity, less important for substances of low specific activity like natural uranium.^(b)

Thus, we need to know even more about a radioactive aerosol than one whose effect is largely due to chemical toxicity (Stannard and Morrow 1956).

g. Monodisperse Aerosols

It has become possible to prepare monodisperse aerosols of various particle sizes. These are very convenient when an experiment is desired without the complications of a range of particle sizes. The generators for these aerosols are described by Mercer (1973) among others. The methodology includes atomization of latex particles, which can be obtained in quite uniform sizes (more in connection with Lovelace).

h. Polydisperse Aerosols

The polydisperse aerosol still occupies a key position. It should, since this is the form in which "real-life" exposures take place. A conscious decision was made for the centers, to be described in the next section, to use polydisperse aerosols at Hanford and at most of the other centers with definitive work on the monodisperse variety centered at Lovelace. The designs of Dautrebande (1962); Lauterbach, Hayes, and Coelho (1956); and a modification termed the Lovelace generator are the most generally used (Mercer, Tillery, and Chow 1968). Diagrams of these are in Mercer, Tillery, and Chow (1968); Bair (1970); and the original publications.

(a) Modern work in chemical toxicology and air pollution indicates that vector aerosols may be more common than suspected.

(b) This contribution alone is probably enough to justify the emphasis on aerosol science in the inhalation programs. Incidentally, it seems to have come in part from examination of radon daughter aerosols (chapter 3) and the wide variations in specific activity seen in fallout particles (Williamson 1957; Farlow and Schell 1957).

C. The Naval Radiological Defense Laboratory

The origin and mission of the Naval Radiological Defense Laboratory (NRDL), which started in the late 1940s, are described in chapters 12 and 13. As a part of this laboratory's general examination of the consequences of radioactive fallout, it carried out a few inhalation experiments, which were done primarily by Dr. Stanton Cohn and his colleagues, especially J. K. Gong. Mice were exposed by the nose-only procedure to fallout simulant aerosols under different conditions of solubility. For the dry particle aerosol, uranium was irradiated by neutrons in the Materials Testing Reactor at Idaho Falls, the resultant mixed fission products were dissolved in acid and then added to a solution of ambrose clay loam (fancy dirt). The average diameter of the dirt particles was $1\ \mu$ to $5\ \mu$, and the fission products were adsorbed on their surfaces. The exposures took place two days after removal of the irradiated uranium from the reactor. Therefore, the very short-lived and gaseous fission products played no role in this experiment.

Cohn et al. (1957a) reported phased clearance of the inhaled material from the lung, largely to the gastrointestinal tract, but with some going to liver, skeleton, thyroid, and head. A separate measurement was made of absorption from the gastrointestinal tract, and it was found to be significant (i.e., enough to account for one-half of the tissue burdens) and considerably more rapid than absorption from the respiratory tract. A simulant in ionic form, reported upon earlier (Cohn et al. 1955), and an ionic-mud slurry were compared to the dry particle simulant. The results were interesting and somewhat unexpected. The highest tissue activities expressed as a ratio to the activity in the respiratory tract occurred after inhalation of the dry particles and the lowest after inhalation of the ionic simulant. The loss rates from the tissues suggest that a few components of the mixtures predominated so that the activity in tissues fell more or less exponentially with time. The highest dose per gram of tissue was to the thyroid in the early hours. Over an extended period, bone would receive the largest integrated dose. Both of these findings are premonitory to simplifications of the dosimetry adopted in the later work with fallout.

While the animals were exposed only to the aerosol, calculations were made of the external radiation dose that might have occurred had there been submersion in a cloud of the same composition. With 2π geometry, the external dose would exceed the internal by a factor of eight, but the internal dose rate would fall off more slowly and be of importance at later times after exposure.

In a companion report, Cohn et al. (1957b) reported on the metabolism of inhaled aerosols of radiostrontium and radiolanthanum. Results with strontium were similar to those already described from the war work, except that bone took up activity so rapidly that it exceeded lung even 0.5 hr after exposure. (And this was for a dry particle aerosol!) With a liquid aerosol, body and bone absorption was even greater. Lanthanum, on the other hand, penetrated to internal tissues hardly at all. This sharp contrast in behavior of these two radionuclides was indicated by the wartime work, but was especially striking in the NRDL experiments.

Except for some work on radon, discussed in chapter 3, these studies, i.e., mixed fission products in a sea-water aerosol, in a mud slurry, and as dry particles, and the work with strontium and lanthanum constitute all of the actual inhalation experiments done at NRDL. However, the laboratory played a very active role in general analyses of fallout problems in the several Congressional hearings we will look at in chapter 12. At one of them, Stanton Cohn (1959) evaluated the hazard for inhaled radioactive fallout. He concluded that the

radiation dose from internal sources would be quite small compared to the external dose. Iodine in the thyroid was the only potential exception.

IV. Maturation: The Genesis of Centers for Pulmonary Radiotoxicology^(a)

A. Hanford/Pacific Northwest Laboratory

The salient features of the development of the Biology Operation at Hanford under General Electric Company management were set forth in chapter 8. The major biomedical programs with radioactive materials, except those involving pulmonary radiotoxicology, were also described there. However, the omission of the inhalation toxicology work was a major one, for in the postwar years Hanford and its successor, PNL, became a major center for such work. Indeed, for many years, until the Lovelace program was fully developed, it preempted the entire field in terms of facilities, personnel, and commitment to inhalation problems.

1. The Early Phases

The inhalation program at Hanford seems to have started by placing a few mice in the atmosphere of a chemical processing plant expected to contain radioactive particles. It gained urgency with the discovery of "hot particles" of ruthenium and other radioelements in the plant environs and the known releases of radioiodine vapors from the stacks.

A more formal effort was organized in the early 1950s under the title "Pharmacology Operation." Dr. Ralph Wager headed it with collaboration especially from D. H. Willard, L. A. Temple, V. Smith, and N. L. Dockum. The work was done in a Quonset hut not far from the facilities developed for the Biology Operation in the so-called 100-F Area, thirty miles north of Richland along the Columbia River. An old photograph of this Quonset hut facility is shown as figure 9.12.

The program concentrated on introducing the relevant radioelements to animals by the technique of intratracheal instillation. There was not time to wait for the development of safe and effective means of producing aerosols of radioactive materials with good control of dosage.

Wager and his colleagues produced the first clear demonstration of lung cancer from plutonium—squamous cell carcinomas in mice that had received $\text{Pu}(\text{OH})_4$ or PuO_2 particles from eleven to seventeen months previously. This was reported in the Biology Research Annual Report for 1955 (Wager et al. 1956). Ruthenium-106 particles given in the same manner produced only necrosis and fibrosis of the lung. The squamous cell carcinomas^(b) appeared in three of ten mice examined one year after intratracheal injection of 0.06 μCi PuO_2 . Autoradiography demonstrated the association of these and other lesions in the lung with the presence of radioactive particles. This was a first for plutonium, to be put beside the first for cerium reported by Lisco and Finkel (1949).

(a) The several centers are introduced in the approximate order of their entry into the field or their maturity at the beginning of the post-World-War-II period.

(b) Just to be sure, the diagnosis was confirmed by the dean of experimental radiation pathologists and director of the AEC Division of Biology and Medicine, Dr. Shields Warren.

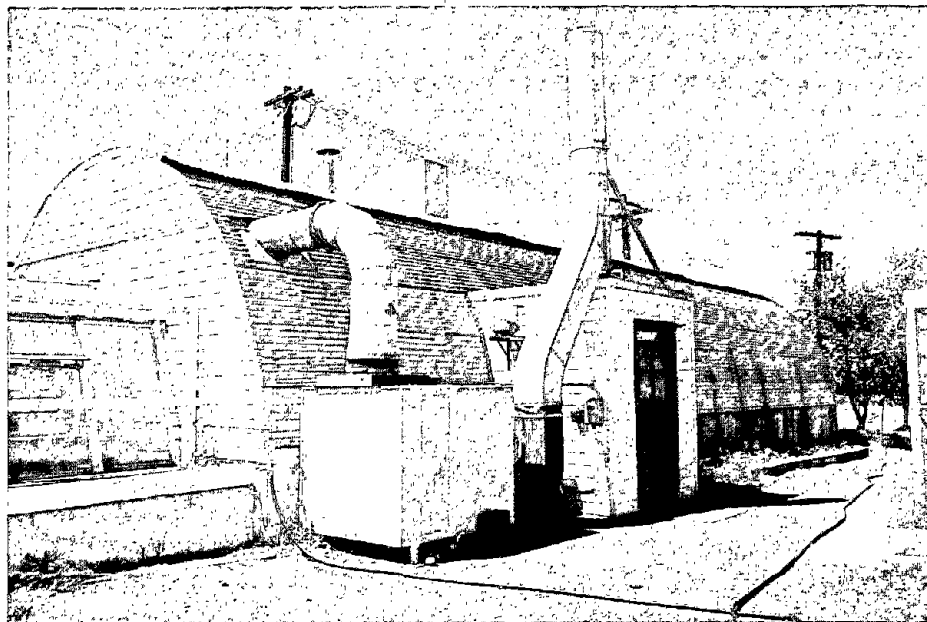


FIGURE 9.12. The original hutment for the "Pharmacology Operation" where the Hanford pulmonary radiotoxicology program started. (Photo courtesy of Pacific Northwest Laboratory.)

Wager et al. describe the role of phagocytes, the aggregation of plutonium in the lung, and other phenomena in the reports for 1954 and 1955. This includes a method for quantitative autoradiography of ^{106}Ru particles in lung tissue (Dockum and Healy 1955).

2. A Commitment is Made

Ralph Wager died unexpectedly in 1956 leaving the fledgling inhalation program at loose ends. A couple of years previously, Dr. William J. Bair had come to Hanford with a Ph.D. in radiation biology from the University of Rochester.^(a) He came to Hanford to continue work on radiation effects in yeast and other microorganisms with Dr. Frank Hungate. However, he had been through the Rochester program with a thorough drilling in the industrial hygiene course by both taking it and helping to teach it. This was enough to give the Hanford people confidence that he could take over and develop their inhalation toxicology operation (officially still "Pharmacology Operation"). Bill Bair was amazed when he was requested to do so but accepted nevertheless, threw his considerable energies into the operation, and quickly developed an effective and creative organization. The problems posed by General Electric and the past experiences of the plant were largely practical, and the Pharmacology Operation

(a) Dr. Bair was the first student in the world to receive a Ph.D. in the new and growing discipline of radiation biology. He was also the first Ph.D. student to do thesis research under the general supervision of this author. His career and contributions make me especially proud to have had an opportunity to help him get started.

tackled these with dispatch. Development of techniques for aerosolizing radioactive materials progressed rapidly. By 1958, reports were appearing that involved administration of aerosols of radioactive particles of ^{106}Ru , ^{239}Pu , ^{90}Sr , and ^{131}I (Bair et al. 1958; Willard and Bair 1958). The first paper is a summary review prepared for the first International Congress on Radiation Research held at Burlington, Vermont. It gives little experimental detail. However, such detail can be found in the Japanese lectures already cited (Bair 1970).

Retention, distribution, and excretion were compared in mice with unexpected results. For example, whole-body retention of plutonium, ruthenium, and strontium were approximately the same, whereas pulmonary retention of strontium was much shorter than for plutonium and ruthenium. A peculiarity of these experiments was the considerable translocation of the inhaled particles to ovary. This was sufficient to raise the question of using ovary as critical organ in computing allowable air concentrations for it. The observation does not seem to have held up consistently in later work at Hanford, however, for the point is not reiterated.

It was too early to expect long-term effects in these animals, but the authors fell back on further effects appearing in the animals that had received intratracheal instillations. Malignant lung tumors appeared in the animals receiving ruthenium dioxide as well as those receiving plutonium. Thus, the roster of radioactive elements producing lung tumors was steadily increasing.

The Willard and Bair work (1958) contains some key findings relevant to all of pulmonary radiotoxicology, as well as to the long-standing questions of inhaled iodine. They compared in mice the biological fate of ^{131}I inhaled as a vapor with an insoluble particulate, silver iodide (Ag^{131}I). The latter is not only the most insoluble compound of iodine (in water) but among the more insoluble substances known. The idea was that the vapor would be rapidly absorbed and excreted and some would be deposited in the thyroid, while the Ag^{131}I would hang up in the lung and provide a base for studying the effects of ^{131}I in the lung. The results were a total surprise. While the percent deposition of the vapor was far ahead of the silver salt (70% versus 12%) both left the lung rapidly and appeared in blood, liver, spleen, kidney, adrenals, and, of course, thyroid. The retention half-time in lung was so similar for the two forms that it was decided it represented only blood retention time.

The comparative deposition and kinetics of retention of these two forms of inhaled iodine are shown in figure 9.13, taken from the Hanford report.

Clearly, the differences in transport are far less marked than the differences predicted by the water solubility of the two substances. This led the authors to caution all workers in inhalation toxicology of the pitfalls of basing predictions or calculations of Maximum Permissible Concentrations on solubility of a compound in pure substances rather than in tissue fluids. This has been going on ever since. Much aerosol work has addressed the problem as discussed in other portions of this chapter. We are still being surprised by the unique properties of body fluids.

Since the generator for iodine vapor and the dry box are of an early design, they are pictured below as figure 9.14A and B.

This work was published in the open literature three years later (Willard and Bair 1961) with the addition of experiments on sheep. There were problems with the Ag^{131}I aerosol in the experiment with sheep, but by turning to oral, subcutaneous, and intraperitoneal routes, they got a reasonable comparison of vapor and particles in the sheep. Again, all major metabolic parameters were similar for the two forms, even among the several routes of administration.

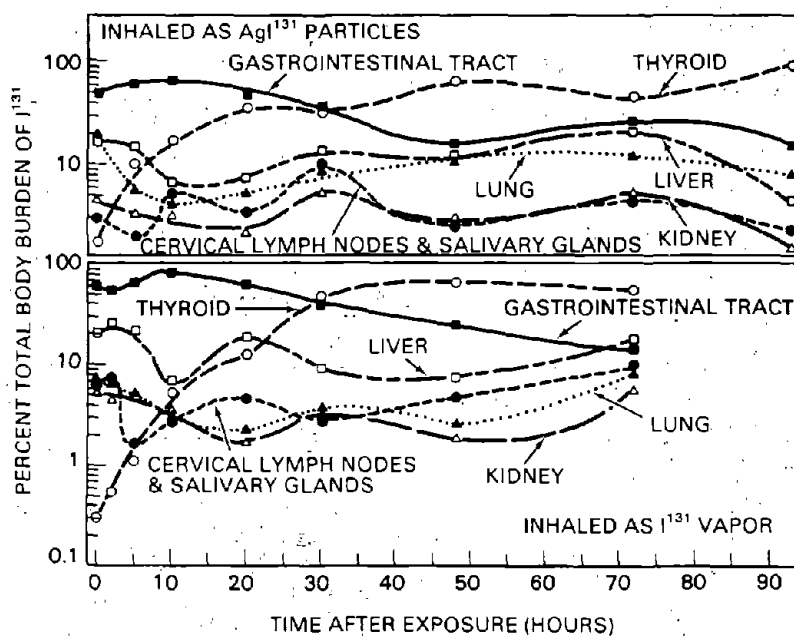


FIGURE 9.13. Relative distribution of I^{131} in mouse tissues. (Redrawn from Willard and Bair 1958.)

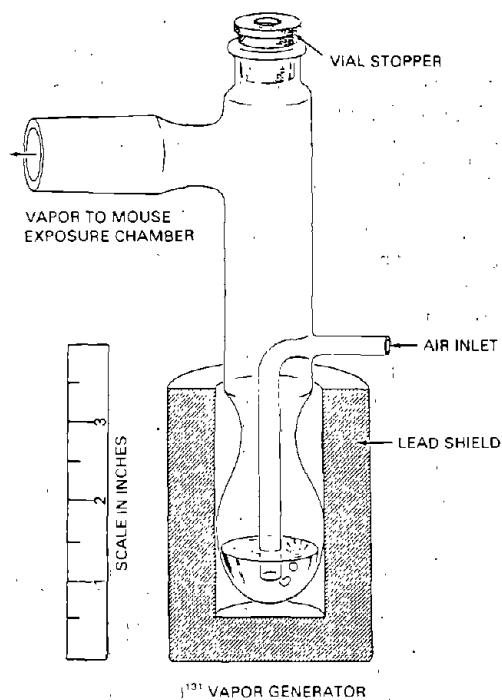


FIGURE 9.14A. Iodine-131 vapor generator. (Redrawn from Willard and Bair 1958.)

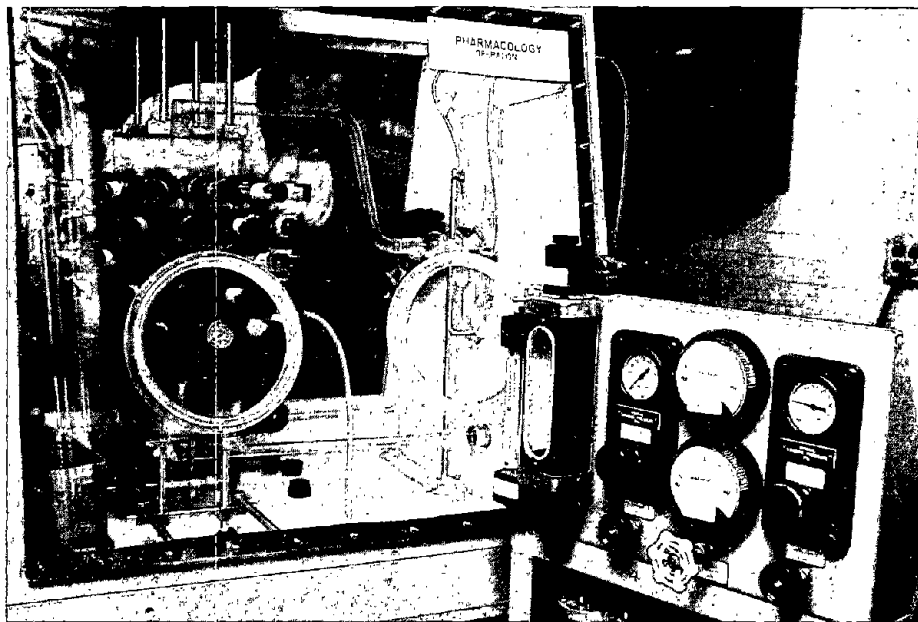


FIGURE 9.14B. Mouse exposure chamber within a glove box for exposure to iodine. (From Willard and Bair 1961.)

The conclusions were that iodine will usually be rapidly absorbed and transported, quickly excreted, temporarily deposited in some soft tissues, but primarily in the thyroid, which is the critical tissue under all conditions. Further work was done at Hanford on inhaled iodine, but it is more pertinent to reactor problems, which we will consider in the next chapter.

Other reports during the first few years of the Hanford inhalation operation concerned the pharmacokinetics of ruthenium particles and plutonium oxide given intratracheally (Willard, Temple, and Bair 1957; Bair 1958). It is interesting to find our old friend, the power function of time, which we had much occasion to discuss in connection with radium, turning up in the whole-body turnover of ^{106}Ru in mice, but with two phases rather than a single line and the more rapid component occurring later rather than earlier. This somewhat unique relationship is shown in figure 9.15.

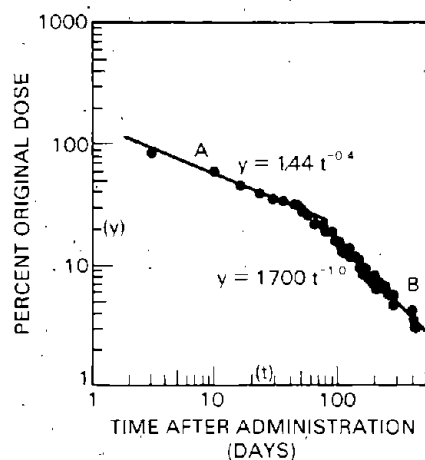


FIGURE 9.15. Whole body turnover of Ru^{106} in mice. (Redrawn from Willard, Temple, and Bair 1957.)

Each annual report brought expanded and more sophisticated discussions in pulmonary radiotoxicology. In addition to the experimental reports, Bair lost no opportunity to prepare definitive reviews of the entire field and present them at the growing number of symposia being held. Samples of these are the International Congress on Radiation Research in 1958 (Bair et al. 1958), the review at the symposium on Radioisotopes in the Biosphere (Bair 1960), the one on Inhaled Particles and Vapors (Bair 1961), the IAEA meeting on Diagnosis and Treatment of Radioactive Poisoning (Bair, Tombropoulos, and Park 1962), and the IAEA symposium on Radiological Health in Mining and Milling of Nuclear Materials (Bair et al. 1964).

Thus, within five years, not only was Hanford committed fully to an ongoing program in pulmonary radiotoxicology, but Bill Bair and his staff^(a) had made a sophisticated and systematic start on many of the problems that had been hanging fire since the early days of the Manhattan District. The technical problems of producing radioactive aerosols safely, reproducibly, and in sufficient quantity for effects as well as tracer-level work were being solved and the ground prepared for long-term studies.^(b)

Naturally, the group outgrew the Quonset hut facility in short order. Sprawling one-story buildings multiplied adjacent to the area used for the sheep work discussed in chapter 8. These could contain exposure chambers, animal test and care facilities, and even an office or two. However, conference and library facilities were still in the relatively close (except on the occasions of Richland's winter fogs) facilities in the Biology Building. All were in the 100-F Area where they had started. There was room to sprawl and no worry about space for animals. But it was not an environment conducive to lunch-table philosophical conversations, for the need to get into and out of protective clothing and the rule of having no food within any potentially radioactive area, restricted academic informality.

A photograph of this facility taken near the zenith of the development in the 100-F Area is given as figure 9.16.

3. Plutonium Takes Over, Almost

Whereas the inhalation program from its inception to the early 1960s was somewhat diversified in that a number of different elements were under study, the next decade saw a major portion of the effort concentrated on the inhalation toxicology of plutonium.

The wartime mission of Hanford was the production and purification of plutonium. The hazard of ultimate concern was the long-term toxicity of inhaled plutonium. With additional laboratories at the animal farm completed, the

(a) Among the new staff that joined the inhalation program in these years were two more products of the University of Rochester: D. K. Craig, whom we met in the section on aerosol science, and Bruce O. Stuart. Stuart, like Bair, did his research under the general guidance of this author, again in fundamental cellular radiobiology. He, too, had taken and helped teach the industrial hygiene and toxicology course. It began to appear that going through the Rochester program was enough to qualify any student for work in pulmonary radiotoxicology and that the thesis subject could be in quite another area without detracting from the potential for such work!

(b) In contrast to the earlier efforts with uranium at Rochester, which involved materials of low specific activity, this work involved materials with much greater hazard potential, particularly for work involving large numbers of animals.

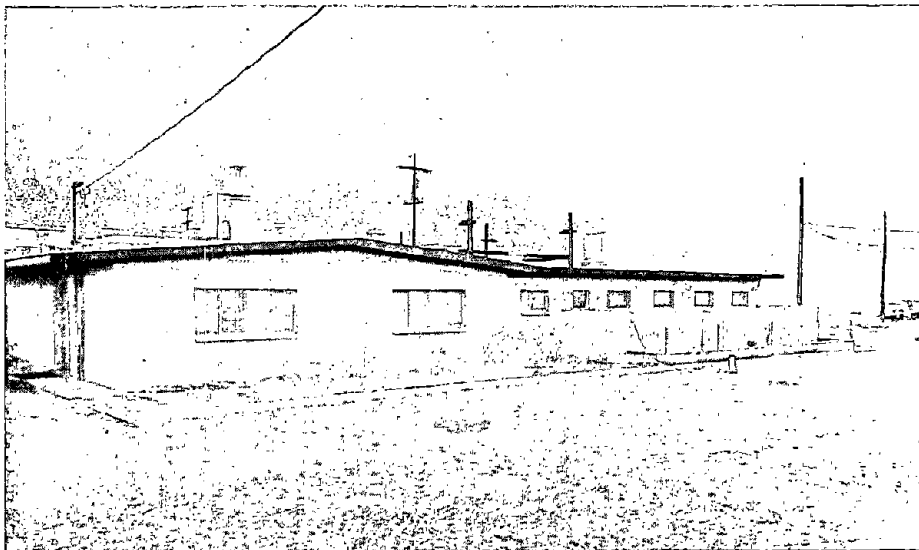


FIGURE 9.16. Photograph of 100-F Area inhalation toxicology facilities at Hanford. (Photo courtesy of Pacific Northwest Laboratory.)

major problems of handling plutonium aerosols and its measurement *in vivo* overcome, the problem could be attacked broadside. First, the acute toxicity; influence of chemical form; and particle size, retention, distribution, and excretion needed study or rechecking. Then a long-term experiment could be begun. (Actually some of these efforts went in parallel, of course.) Mechanisms could get more attention.

Diversification increased rather than decreased in this period because the plutonium problem developed in its own right into several subproblems, and new aspects of its use caused considerable pressure from Headquarters to embark on new semiapplied pathways. Also, the U.S. Air Force became quite interested and actually supported the first dog studies.

One of these was the "Space Nuclear Systems" work, which will be discussed in section V C. Another concerned some medical applications extending to americium and californium (Seaborg 1973). For many years, the inhalation toxicology group reported some of its work regularly under the title "Space Nuclear Systems Studies." The devices were a joint development of AEC, the National Aeronautics and Space Administration, and the Department of Defense, but biomedical aspects resided in AEC.

In due course, experimental work on the uranium mining problems, discussed in chapter 3, came to Hanford with emphasis on possible additive or synergistic effects of cigarette smoke, uranium ore dust, and diesel exhaust fumes.

Threading through all of this work were studies aimed primarily at mechanisms.

Some of the attempts at therapeutic removal of deposited radionuclides alluded to in chapter 8 and slated for details in chapter 19 were directed at removal of radioisotopes, particularly plutonium, from the lung.

Obviously, the program was growing quite beyond the times when Bair and a few colleagues and technical assistants could handle it all. A degree of specialization and compartmentalization had to develop. Yet, to the credit of those responsible, most of the senior staff had a finger in several of the projects and could at the same time develop their own interests. We will review very briefly below what went on in these various areas, who was primarily concerned, and the highlights of the results. Since the literature is very complete and largely accessible, excessive details will be avoided.

Before attempting this review, we should pause to note the 1964 Hanford symposium on Inhaled Radioactive Particles and Gases. An indication of the rapid maturation of the Hanford inhalation program was their sponsorship of this full-dress symposium on 4-6 May 1964.^(a) There were over 160 visiting scientists from nine countries and 180 Hanford scientists participating. Nearly every major laboratory doing pulmonary radiotoxicology was represented, and papers were presented from most. About a fifth of the papers were from the Hanford program, a fine showing for an enterprise begun less than eight years before. The symposium was published in *Health Physics* as Volume 10, Number 12 in December 1964 (see Hanford symposium listings in chapter 8).

- a. **Long-term Studies with $^{239}\text{PuO}_2$** ^(b) (W. J. Bair, J. F. Park, B. O. Stuart, W. J. Clarke, C. L. Sanders, D. K. Craig, P. L. Hackett, E. B. Howard, H. A. Ragan, and others.)

The most extensive inhalation studies with dogs used $^{239}\text{PuO}_2$ prepared by calcining the oxalate at about 350°C.^(c) Particle size was 0.3 to 0.5 μm count median diameter (CMD), about 3 μm MMD. About one hundred dogs were exposed to from less than 1 μCi to 50 μCi . The latter caused early acute effects. The basic experimental protocol had four phases:

1. pre-exposure phase—training of dogs for the aerosol exposure, complete physical examination, establishment of physiological base lines, and acclimatization to the metabolism cages
2. exposure phase—a single exposure lasting from ten minutes to two hours; respiratory parameters measured
3. metabolism-cage phase—for varying periods for collection of excreta, plus periodic measurements of other parameters
4. sacrifice/euthanasia phase—metabolism animals killed on a predetermined schedule or when toxicity made euthanasia advisable. Other animals were set aside for long-term observations. Hematology, roentgenography, and many other interim procedures were applied regularly. Plutonium retention was generally logarithmic to time over the long haul, and loss, once the rapid phase was over, was slow. Some organs gradually accumulated plutonium but took from two to four years to approach significant translocated amounts. Liver and bone continued to increase as fraction of the body

(a) This was the third Hanford symposium; see chapter 8.

(b) This program was started when the General Electric Company was still operating Hanford, but it ran far into the era of Battelle sponsorship. Indeed, it is still under way. The transition took place in 1965.

(c) Other forms were compared. This one showed greatest accumulation in the tracheo-bronchial lymph nodes and relatively rapid clearance from the lung.

burden as long as tissue content measurements continued. These were extrapolated to as long as fifteen to twenty years by a computerized simulation model.

The model and the extrapolated tissue contents are shown in figure 9.17A and B.

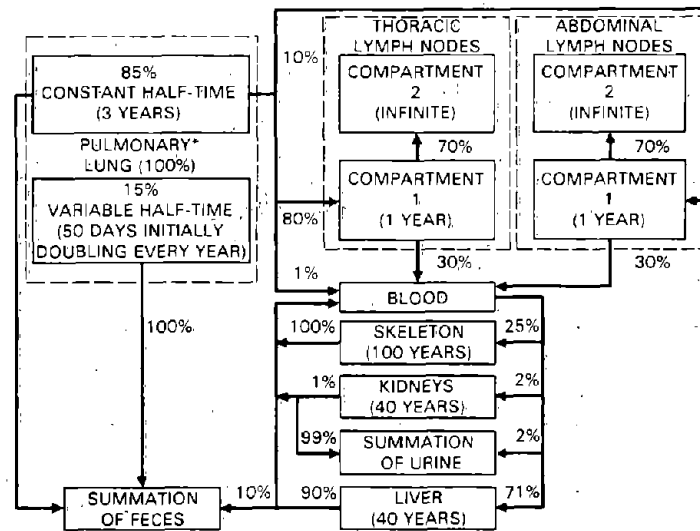


FIGURE 9.17A. Long-term dynamic simulation of inhaled $^{239}\text{PuO}_2$ (half-times in parentheses). (Redrawn from Stuart, Dionne, and Bair 1971.)

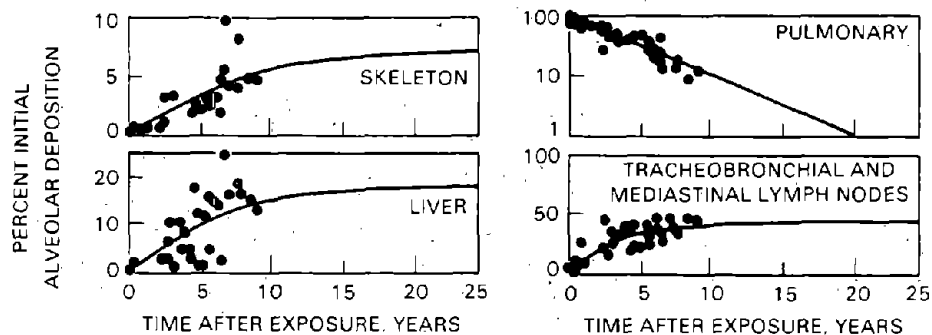


FIGURE 9.17B. Long-term tissue burdens of plutonium after inhalation of $^{239}\text{PuO}_2$. Points from experimental data, lines from model shown in part A (Modified slightly from Stuart, Dionne, and Bair 1971.)

The effects of inhaled plutonium vary with dose, of course, and there is much overlap among categories of pathology. A representation used by the Battelle group on several occasions is given in figure 9.18.

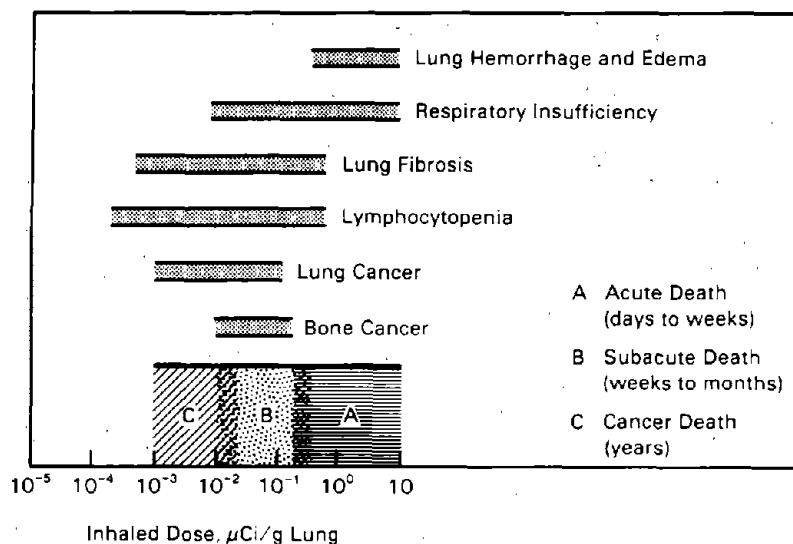
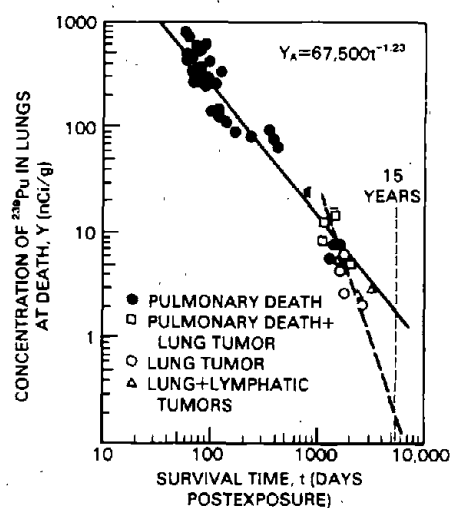


FIGURE 9.18. Observed biological effects of inhaled plutonium. (Redrawn from Bair 1974; also ICRP 1980, figure 9, p. 37. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1974.)

Translated to initial deposition in the pulmonary compartment of the lung, it appears that acute death can occur in the range from $10 \mu\text{Ci/g}$ to approximately $10^{-1} \mu\text{Ci/g}$, subacute death in the range from $3 \times 10^{-1} \mu\text{Ci/g}$ lung to $3 \times 10^{-2} \mu\text{Ci/g}$, and carcinogenic death in the range from $3 \times 10^{-2} \mu\text{Ci/g}$ lung to $3 \times 10^{-3} \mu\text{Ci/g}$ lung. (a)

A somewhat different relationship, which shows also the effect on survival time, has been presented by Bair and his colleagues on several occasions. An example, taken from Bair's lecture series in Japan, is shown as figure 9.19. Here the lowest effective dose is about 2 nCi/g lung at death.

FIGURE 9.19. Relationship between quantity of ^{239}Pu in lung at death and survival time of dogs. (Redrawn from Bair 1970.)



(a) The lower figure of the range may not be a minimum.

Numerous dose-response relationships have been drawn as this long-term experiment unfolded. These relationships are expanded upon in depth in the ICRP publication, *Biological Effects of Inhaled Radionuclides* (ICRP 1980). Here the graphs include not only Hanford and other U.S. data (including PNL and Lovelace data on hamsters), but work from France and the Soviet Union on rats. A few points fall squarely on the abscissa (i.e., no effect). However, this work goes well beyond the period of our present interest.

Bair (1970) calculated the lung burden that was unlikely to produce either cardiopulmonary insufficiency or lung tumor as less than 0.5 nCi/g lung.

b. Influence of Particle Size (Matsusaka, Park, Willard, Bair)

A concise summary of the beagle experiments as of the early seventies is given by Park, Bair, and Busch (1972).

Despite the backlog of information from industrial dust exposures and other radioactive isotope inhalation work, it was necessary to check out influences of particle size in plutonium aerosols under the conditions of these experiments. Plutonium was hardly an ordinary industrial dust.

The effects of particle size on deposition and clearance were found to be broadly consonant with the behavior predicted by the uranium experiments at Rochester. Deposition showed an unexpectedly large difference between two fairly similar aerosols (Bair and Willard 1961). Clearance from the lung was much more rapid and complete for an aerosol with mass median diameter of $0.65\ \mu$ (0.086 CMD) in contrast to either $3.3\ \mu$ MMD or $4.3\ \mu$ MMD, but translocation to other tissues was not uniformly affected. Both PuO_2 and PuHO_3 were used, and the results were surprisingly comparable.

Very complete analyses were made of excretion kinetics. The results are best seen in Bair's lectures in Japan (Bair 1970). On the whole, the predictions of earlier work were realized.

Some work was done with ^{238}Pu as well as ^{239}Pu . Unexpected differences were found, but in this particular work the radiation dose from the ^{238}Pu isotope was quite high and may have complicated the results.

c. Effect of Chemical Form (Dilley, Park, Stuart, Willard, Bair)

Radioisotope toxicology has, in general, needed to concern itself less with the nature of the compound than counterpart work in chemical toxicology. Some special situations apply to plutonium. It was known that plutonium encountered occupationally or in the environment might have been through one of several processes, even if it was nominally PuO_2 , e.g., calcining of the oxalate or metal at different temperatures. Or, different compounds might be present, e.g., PuF_4 and $\text{Pu}(\text{NO}_3)_4$. The different treatments and their effects are described by Bair and Park (1968). A sample of the findings is shown in figure 9.20.

It is clear that: (1) the half-times for PuF_4 and $\text{Pu}(\text{NO}_3)_4$ in the whole body are distinctly shorter than for the "less soluble" PuO_2 , even at smaller particle sizes; (2) ^{238}Pu appears to clear more rapidly than ^{239}Pu , but this may have been a particle-size effect; and (3) differences in chemical form of PuO_2 make considerable difference in retention. Indeed, the differences in chemical form can override differences in particle size. Effects of similar magnitude apply to translocation from lung and behavior in tissues. Autoradiography demonstrated differences in the size and location of the "stars." However, this effort, which was extensive, is too specialized to warrant further exposition here. Suffice it to say that this work alerted all concerned with the evaluation of hazards to the fact

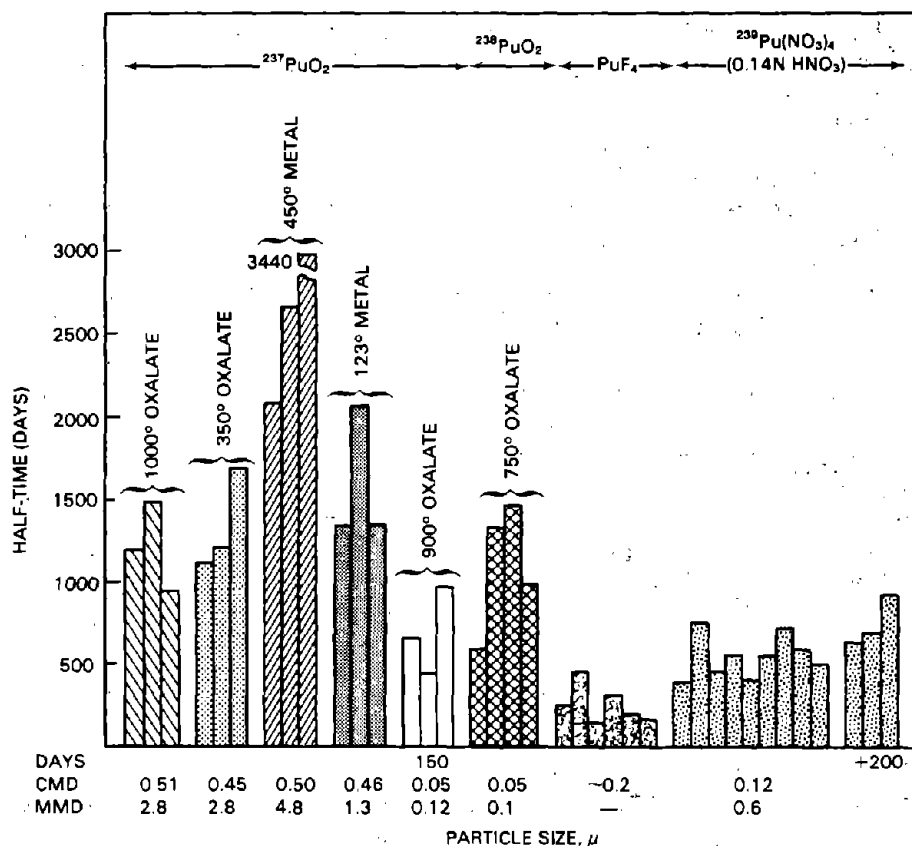


FIGURE 9.20. Summary—whole-body retention half-times for inhaled plutonium in dogs. (Redrawn from Bair 1970.)

that it was necessary to know in some depth the origin of any plutonium available for inhalation before quantitatively reliable evaluations could be made. Also, it pointed up possible explanations for “aberrant” and puzzlingly inconsistent results of the past.

The basic biomedical fact that the organism can distinguish between and handle differently particles of apparently the same size distribution but subtly different in physicochemical composition bespeaks the need for further sophisticated experimentation at the basic level.

d. Plutonium-238

Even before the advent of Systems for Nuclear Auxiliary Power (SNAP) devices (see section V C) and of microspheres of ^{238}Pu , there were indications that the shorter-lived isotope (86.4 yr for ^{238}Pu versus 24,390 yr for ^{239}Pu) behaved differently in vivo. It seemed to be more transportable, aggregates disintegrated spontaneously, and even ultrafilterability of the particles was different and changed with time.

The work on SNAP devices at Battelle, supported in part by the Air Force, involved characterizing the behavior of the ^{238}Pu microspheres, particularly when crushed in simulation of their breakdown in a re-entry incident, and generally comparing the biomedical problems of ^{238}Pu and ^{239}Pu . The results showed that a simple scaling factor based on half-life and specific activity would not predict behavior or toxicity on inhalation.

Stuart (1970) reported that, while the basic pattern of movement from lung to skeleton in rats and to lymph nodes and liver in dogs was not different for ^{238}Pu , there was more ^{238}Pu in the skeleton and in the liver in the rat. The magnitude of the differences is considerable, as shown in table 9.7A and B, modified by D. M. Taylor from Stuart's work.

TABLE 9.7A. Tissue Distribution of ^{239}Pu in Rats After Inhalation of $^{239}\text{PuO}_2$ (percent of body burden at death)

Rat No.	Days After Exposure	Skeleton	Liver	Spleen	Lungs	Tracheobronchial Lymph Nodes
95	7	0.01	0	0	67	0.1
63	13	0.01	0.02	0	97	0.3
73	28	0.1	0.4	0.02	96	1.4
30	68	0.1	0.3	0.04	97	1.8
4	113	0.2	0.3	0	99	—

TABLE 9.7B. Tissue Distribution of ^{238}Pu in Rats After Inhalation of $^{238}\text{PuO}_2$ (percent of body burden at death)

Rat No.	Days After Exposure	Skeleton	Liver	Spleen	Lungs	Tracheobronchial Lymph Nodes
84	20	11	2.4	0.1	82	0.4
67	48	12	1.3	0.2	84	0.6
39	78	23	1.9	0.2	77	0.8
50	127	15	1.7	0.2	78	3.4
59	320	30	1.6	0.7	64	3.3
5E	465	48	3.6	0.6	40	0.1
4E	481	23	3.6	0.5	68	3.3

Source: Reset from Taylor 1973b, which was taken from Stuart 1970. Reprinted with permission of Springer-Verlag, Heidelberg, copyright 1973.

Toxicity studies did not indicate differences beyond those expected from the 282-fold difference in specific activities ($6.12 \times 10^{-2} \mu\text{Ci/g}$ for ^{239}Pu versus 17.4 Ci/g for ^{238}Pu). At one of the numerous SNAP-SNPO meetings held in Washington, Bair (1967) gave acute mortality data for $^{238}\text{PuO}_2$ and $^{239}\text{PuO}_2$ in rats and dogs (see also Park, Howard, and Bair 1970). On a microcurie basis, the two isotopes were about equally effective. Published papers (Stuart et al. 1968; Park et al. 1970) confirmed these findings. There were, however, differences in distribution between ^{238}Pu and ^{239}Pu , as mentioned earlier.

Since there were no long-term low-level experiments completed at the time with ^{238}Pu , Bair (1967) engaged in calculations based on the relative radiation dose around a $0.25\text{-}\mu$ particle of each isotope. Since the much larger dose from

^{238}Pu would be much more likely to be a sterilizing dose, he predicted that ^{239}Pu would be more carcinogenic than ^{238}Pu as long as the dose was large enough to be significant.

A special side study on particle-size effects was possible with the microspheres. Many of them were well above the theoretical cutoff point for "respirable size," viz., $10\ \mu$ to $20\ \mu$. An experimental double check was instituted since the literature seemed to be more theory than practice on the point, or so the investigators felt. They found that $15\text{-}\mu$ particles or larger did indeed never get below the nasopharynx. They were deposited there but rapidly moved to feces. Since then, quite large particles, up to $300\ \mu$, have been placed in animals' lungs by intratracheal instillation. They have remained in situ for many years with relatively little evidence of pathological effects except locally.

In summary, it was clear from the work cited (and it has continued) that there are real differences between the two major isotopes of plutonium (-238 and -239). The ^{238}Pu isotope is more mobile. There is relatively less retained in lung, even with nominally the same chemical forms, and more transferred to bone. These differences and the others make for a potentially different long-term risk from comparable initial activity levels (Bair, Park, and Clarke 1966).

e. Cellular Interactions with Plutonium Particles

This work conducted primarily by C. L. Sanders,^(a) is part of a continuum that it will be more convenient to discuss as a unit in a following section (4 i). Be reminded, however, that a lively program involving the basic interaction between plutonium and biological host cells, particularly macrophages, was under way from the early years of the inhalation program.

f. Nonplutonium Studies

Pulmonary radiotoxicology at Hanford during the decade of the 1960s was, of course, not exclusively devoted to plutonium. There was much carry over from the decade of the 1950s. In chapter 3, we reviewed the quite considerable program in the 1960s and 1970s with radon and daughters and the uranium miner problems. This included some work with thorium (Stuart and Beasley 1967). As part of the therapy program, aerosols of ^{106}Ra , ^{144}Ce , and ^{90}Sr were compared to ^{239}Pu . Americium-241 was studied in part because of its development from plutonium, in part in a separate inhalation experiment aimed at bioassay (Henle and Branson 1969). In the early 1970s, inhalation work with ^{145}Sm and ^{147}Pm and some of the higher transuranics began. We will look at these as part of the next phase.^(b)

4. New Buildings, More Plutonium, More Diversity: The 1970s

Toward the end of the decade of the 1960s, plans were approved to construct a major new facility for the Biology Department in the 300 Area. This was hard by

(a) Charles Sanders is the fourth University of Rochester Ph.D. to become involved directly with the inhalation program at Battelle-Northwest (BNW). Fred Cross, whom we met in chapter 3, also came from Rochester but worked in another division at BNW until his association with the uranium miner work drew him into the inhalation toxicology fold.

(b) Remember, of course, that noninhalation work with many radionuclides was going on in parallel during these years of concentration in the inhalation program on plutonium.

the outskirts of Richland on a beautiful site overlooking the Columbia River. In 1970, the process of moving most of the operation from the outlying 100-F site was completed. The new Life Sciences Laboratory was dedicated in 1971 with historically significant remarks by John R. Totter, director of the AEC's Division of Biology and Medicine; by H. M. Parker, former director of the Hanford Laboratories; and by H. A. Kornberg, who managed the Biology Department for the twenty years from 1948 to 1968 and later was Associate Manager of the Environmental and Life Sciences Division. These are reproduced in the annual report for 1971, published in September 1972 (PNL 1972).

The emphasis on pulmonary radiotoxicology went undiminished in this change. In fact, so many new inhalation experiments were planned that, despite the new space, part of the work (e.g., inhaled uranium mine air contaminants) had to remain in the 100-F Area.^(a) A Life Sciences Laboratory II, built by Battelle, was completed about five years later. These two buildings now contain all active work in pulmonary radiotoxicology.

a. A Second Long-Term Study with Plutonium in Dogs

(Park, Dagle, and numerous collaborators)

The work in the earlier long-term dog study and concomitant work with rodents made it clear that a new experiment would be needed at still lower levels of plutonium.^(b) The extraordinary efficiency of plutonium in causing lung damage of all kinds seen in the decade of the 1960s required this. In addition, life-span studies with ^{238}Pu and plutonium nitrate were indicated by the previous work with dogs (relatively short-term) and rodents.

Therefore, an experiment with over 350 beagles was gradually developed with inhalation exposures to $^{239}\text{PuO}_2$, $^{238}\text{PuO}_2$, and $^{239}\text{Pu}(\text{NO}_3)_4$. The principal investigator for the PuO_2 work was J. F. Park, for the plutonium nitrate work, G. E. Dagle.^(c) Exposures began in 1971 and continued through 1977. Total alveolar deposition and microcuries per gram lung were as follows:

	Initial Alveolar Deposition			Dosage Groups
	Number of Dogs ^(d)	nCi	nCi/g lung	
$^{239}\text{PuO}_2$	130	3.5 - 5800	0.029 - 50	6
$^{238}\text{PuO}_2$	133	2.3 - 5200	0.016 - 43	6
$^{239}\text{Pu}(\text{NO}_3)_4$	105	2 - 5445	0.02 - 47	6

Sacrifices for distribution measurements and pathology reduced the life-span study groups to 108, 113, and 87, respectively. Additional animals were exposed as necessary for periodic sacrifice or tissue distribution work.

The progress of this experiment was summarized regularly by narratives in the annual reports, at several symposia, and by detailed tables at the end of each

(a) Some long-term animal farm operations remained at the 100-F site also.

(b) Remember that new lower levels had to be added in the Utah intravenous experiment (chapter 8).

(c) By this time, Bill Bair had become manager of the Biology Department. He, of course, maintained constant interest in the inhalation program but authored fewer of their progress reports. This second long-term study had the benefit of strong support from Chester Richmond, who was at that time at AEC Headquarters.

(d) Without controls.

annual report, much as was done for the Utah experiments.^(a) In addition to the usual hematologic and pathologic observations, many functional observations were made.

Recent summaries of significant lesions seen in the dogs appear in the annual report for 1981. We will depart from our nominal cutoff time to place as complete information as possible in these pages.

Table 9.8A and B show such a summary of the low-level $^{239}\text{PuO}_2$ and $^{238}\text{PuO}_2$ studies in dogs after 10 and 7.5 yr, respectively.

TABLE 9.8A. Summary of Lesions in Dogs Euthanized During the 10-yr Period After Inhalation of $^{239}\text{PuO}_2$

Dose Group	No. Dogs/Group	No. Dead Dogs/Group	Number of Dogs/Lesion Associated with Death											
			Radiation Pneumonitis	Lung Tumor	Malignant Lymphoma	Hemangiosarcoma	Reticulum Cell Sarcoma	Pituitary Tumor	Ovarian Tumor	Oral Tumor	Pneumonia	Thromboembolism	Septicemia	Epilepsy
6	8	8	7	1										
5	21	21	1	20										
4	22	10		6			1	1			2			
3	20	4		1								1		
2	21	2							1					1
1	24	4			1	1					1		1	
Control	20	1								1				

Source: Reset from Park et al. 1982, p. 65.

TABLE 9.8B. Summary of Lesions in Dogs Euthanized During the 7.5-yr Period After Inhalation of $^{238}\text{PuO}_2$

Dose Group	No. Dogs/Group	No. Dead Dogs/Group	Number of Dogs/Lesion Associated with Death									
			Lung Tumor	Bone Tumor	Bone Tumor & Lung Tumor	Bone Tumor & Addison's Disease	Bone Tumor, Addison's Disease & Lung Tumor	Addison's Disease	Hemangiosarcoma, Heart	Pneumonia	Spinal Cord Degeneration	Pyometra
6	13	13	3	2	6	1		1				
5	20	10		5	1		1	2		1		
4	20	1							1			
3	22	0										
2	21	1									1	
1	20	0										
Control	20	1										1

Source: Reset from Park et al. 1982, p. 69.

(a) And, as we will see, for the Lovelace work.

The work with $^{239}\text{Pu}(\text{NO}_3)_4$ is not far enough along to permit a similar tabulation, but Dagle et al. (1982) have presented a summary of both tissue distribution and cause of death in animals up to fifty-nine months after exposure.

The tissue distribution figures are as expected from earlier work with characteristically greater mobility of ^{238}Pu and of the nitrate. *The earliest effect observed with all three compounds was chronic lymphopenia.* This occurred after ≥ 80 nCi of ^{238}Pu or ^{239}Pu in the lung and at higher dosage levels (to date) with the nitrate.

The most striking contrast is the total absence of bone tumors after inhalation of $^{239}\text{PuO}_2$. Lung tumors were numerous, but evidently transport to the skeleton is too low to induce bone tumors in the period under study. With $^{238}\text{PuO}_2$ and $^{239}\text{Pu}(\text{NO}_3)_4$, both bone and lung tumors occurred, some in the same animal.

Obviously, the work is not complete, and the contrast between isotopes and compounds may not be absolute. However, in terms of relative risk, it seems likely that lung will remain at greater risk from $^{239}\text{PuO}_2$. No lung tumors have occurred yet below $77 (\pm 11)$ nCi in lung or $0.56 (\pm 0.07)$ nCi/g initial alveolar deposition of $^{239}\text{PuO}_2$. The final lung burdens are, of course, much lower. There is too much individual variation at the present stage to hazard estimating a mean of the final burdens.

Similar figures for $^{238}\text{PuO}_2$ indicate no lung or bone tumors below $1,300 (\pm 270)$ nCi in alveolar lung or $10 (\pm 1.9)$ nCi/g lung. It is doubtful if this means a lesser effectiveness for ^{238}Pu since the time period is shorter. We must wait out the balance of this experiment to determine minimal effective doses in the dog, if there are any.

The effects of $^{239}\text{Pu}(\text{NO}_3)_4$ are more like those of $^{238}\text{PuO}_2$ in that both lung and bone tumors have already appeared. There were differences in microdistribution in liver between the nitrate and the oxide as determined by autoradiography.

Some cooperative work on bone changes was arranged with the University of Utah to compare the inhalation and intravenous routes of administration.

b. Continued Long-Term Studies with Rodents (Sanders and collaborators)

In addition to the ever-present long-term experiment with dogs, several relatively long-term investigations were conducted with rodents, primarily rats and later hamsters (Sanders and Dagle, 1974).

In a carefully worked-out set of long-term experiments in rats, Sanders (1975a,b) showed that the incidence of lung tumors may be increased following the initial alveolar deposition of as little as 0.15 nCi of $^{239}\text{PuO}_2$. A similar experiment with $^{238}\text{PuO}_2$ showed increased incidence of lung tumors following only 0.07 nCi. Squamous carcinoma predominated at higher deposition levels, adenocarcinoma at lower levels for both isotopes of plutonium. No mention is made of skeletal tumors in these rat experiments.

In work done in 1978, Mahaffey and Sanders (1979) reviewed all of the data on rats (over five thousand animals) for transuranics to extract some risk-estimate figures that could be extrapolated to man. The risk of lung tumors from 1.5 alpha rad per year (the then-permitted dose for occupational exposure) ranged from as high as 1 in 9 to as low as 1 in 120, depending on assumptions. All of these seem unacceptably high.

Multiple exposures to inhaled $^{239}\text{PuO}_2$ were begun by these same investigators in 1978, and studies of the metabolism and late effects of $^{239}\text{PuO}_2$ were initiated in the same year.

The metabolism and late effects of $^{239}\text{PuO}_2$ were compared directly in rats and dogs (Mahaffey et al. 1980). In relation to expected life-span, lung tumors appeared proportionately earlier in dogs than in rats. In this experiment with a direct comparison of a single inhalation exposure to the same aerosol, it also appeared that the dog translocated considerably more ^{239}Pu to thoracic lymph nodes, liver, and skeleton than did the rat at all periods from 15% to 65% of the maximum life expectancy. In fact, liver is *higher* than skeleton in terms of percentage of initial lung burden at all periods in the dog, whereas the two organs are comparable in rats, except for the earliest period (15% to 25% of the maximum life expectancy). This contrasts with some of the MED work.

Sanders has reported on a very low-level life-span experiment in rats (Sanders, Mahaffey, and McDonald 1982). Life-span radiation doses are calculated at from 2 to 100 rad. An interesting twist in this recent work was the addition of ^{169}Yb as a gamma tag for plutonium, an idea generated at the Inhalation Toxicology Research Institute at Lovelace. Despite some dissociation of the ^{169}Yb from ^{239}Pu , reproducible whole-body counts could be obtained at the low levels involved.

The hamsters (Syrian Golden hamsters) were introduced into the plutonium experiments for several reasons: (1) an additional species is always useful; (2) the hamster lung had shown signs of resistance to cancer induction in experiments with radon and radon daughters (chapter 3); and (3) the hamster is less prone to upper respiratory illness, which has always been a problem in rat and mouse colonies. Sanders (1975a,b) used optimal carcinogenic doses for the rat of both $^{239}\text{PuO}_2$ and $^{238}\text{PuO}_2$. There was no question that the pathologic response was different in the hamster. The primary cause of death at the higher doses was radiation pneumonitis, not different from other species—but at lower doses; amyloidosis and chronic nephritis were much more common. While there was considerable pulmonary adenomatous metaplasia in the hamster lung in the highest exposure groups, there was only one primary lung tumor in 172 necropsied hamsters. *The lung cancer resistance seen with other radionuclides thus seemed to extend to plutonium.* The distribution to tissues of the inhaled plutonium was quite similar in rat and hamster. Therefore, the difference in tumor incidence cannot be explained by a difference in tissue content. A full explanation might offer some clues to the mechanisms of carcinogenesis.

c. Exposure of Swine to Plutonium Aerosols

In 1975, work was carried out on techniques for exposure of miniature swine to inhaled aerosols (Karagianes et al. 1976). In view of the central role this animal has played in other Hanford programs, this extension is not surprising. A single exposure to $^{239}\text{PuO}_2$ is reported with results “encouragingly similar” to the distribution pattern established for dogs and rodents. However, the work seems not to have gone much beyond establishing the feasibility of using miniature swine for inhalation work.

d. Plutonium and Cigarette Smoke

We reviewed in chapter 3 some of the Hanford work in which beagles were taught to smoke cigarettes through a mask arrangement. This was especially pertinent because the miners tended to be heavy smokers.^(a) A picture of the special mask assembly is shown in figure 9.21.

(a) This was not universally true, as also discussed in chapter 3.

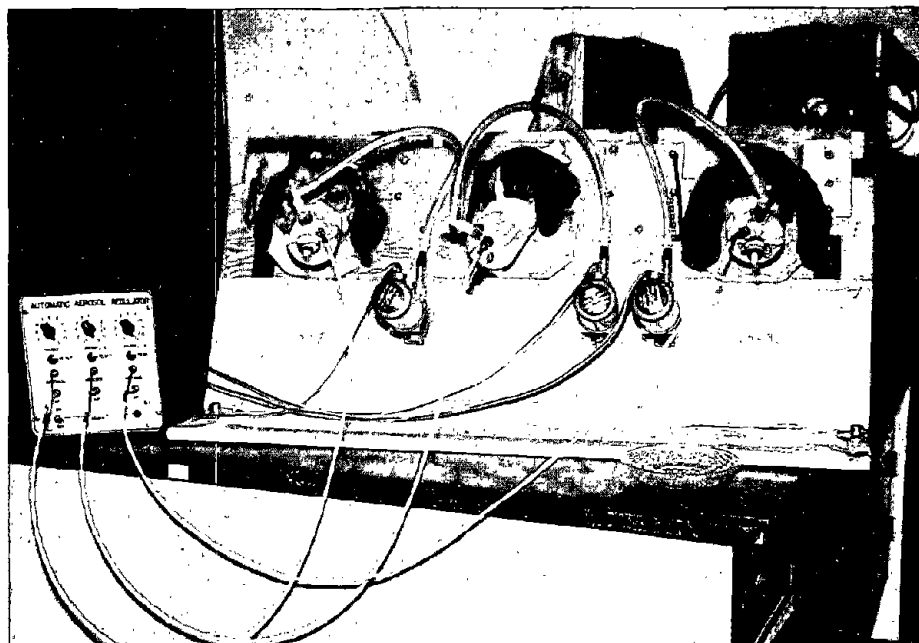


FIGURE 9.21. Mask assembly for the smoking beagles. (Photo courtesy of Pacific Northwest Laboratory.)

The chance of simultaneous exposure to plutonium and to cigarette smoke in ordinary occupational exposure is slight because of the rigid rules against smoking in the work areas and the frequent wearing of face masks. Nevertheless, the possibility that cigarette smoking might alter the lung transport processes, as well as the sensitivity of the critical cells for cancer development, led the Battelle investigators to check out the basic phenomena in both rats and dogs. It is applicable to both occupational and potential population exposures.

It appears that this additional work with cigarette smoke had to await the move to new facilities and lagged considerably behind the companion work with radon, uranium ore dust, and diesel smoke. It was not begun until 1978. In 1980, work on the influence of smoking on plutonium clearance and effects was described in detail. It started with rats (Filipy et al. 1980). For this work, the cigarette smoke was produced by a special device (Walton Smoke Exposure Machine®) and given in ratios of 1/10 of smoke to air. At the end of a seven-month period of exposure to cigarette smoke, one group of thirty-five rats received a single inhalation exposure to $^{239}\text{PuO}_2$ to produce an initial lung burden of 50 nCi. There were, of course, groups receiving only the plutonium and a sham smoke \pm plutonium. The smoke-exposed groups cleared plutonium from the lungs significantly more slowly than the others. The delay in lung clearance would presage a greater risk of lung cancer, unless other factors intervene.^(a)

® Process and Instrumentation Corporation, Brooklyn, New York.

(a) The reported delay in clearance is not consonant with experiments in man, some of which have indicated more rapid clearance in smokers, also increased mucus secretion, both of which might provide protection rather than exacerbation.

A similar experiment with trained beagles was reported (Filipy et al. 1980). The inhibitory effect on pulmonary clearance of $^{239}\text{PuO}_2$ seen in rats was confirmed in the dog. The initial lung burdens were $0.3\ \mu\text{Ci}$ to $1.4\ \mu\text{Ci}$, and a difference in clearance rate between young and old dogs was noted.

Incidental to the development of the work in dogs was the fabrication of a new exposure valve assembly for switching to the lighted cigarette (research cigarettes from the University of Kentucky). In the old system used for the uranium mining work, a solenoid valve was used which produced a loud click on the switch to cigarette smoke. Evidently some of the dogs did *not* enjoy smoking^(a) and learned to use the audible click as a cue to draw only a quick, shallow breath. This quickly switched the valve back to fresh air. By measuring blood levels of carbon monoxide hemoglobin, it was clear that there was considerable variability among dogs in the amount of smoke inhaled. With the newer system, a motorized pump with no cues to help the dogs beat the system, more uniform exposure to the smoke was found.

e. Plutonium-Sodium Aerosols

Toward the end of the decade of the 1970s, the Battelle group attacked questions surrounding the planned liquid metal fast breeder reactor (LMFBR), which uses liquid sodium as a coolant. They engaged in study of both sodium aerosols and of potential mixtures of LMFBR fuel with sodium aerosols. They were not alone in this new work and concentrated on behavior after inhalation.

First, the technical problems were attacked of producing an aerosol that might simulate one produced in possible core melt-down and release of an Na-(PuU)O_2 aerosol into the environment. This was accomplished by laser vaporization of reactor fuel (Briant and Allen 1981).

Biological behavior was looked at in both dogs (Hackett et al. 1981a) and rats (Hackett et al. 1981b). Initial pulmonary deposition was greater for fuel aerosols, but the rate of pulmonary clearance of sodium-fuel aerosols was higher, and larger fractions appeared in blood, liver, and skeleton. Chemical work indicated a solubilization reaction *in vitro* in the presence of sodium. Much less of the sodium-fuel aerosol went to thoracic lymph nodes than from aerosols of fuel without sodium. Results with dog and rat were comparable.

This work is being continued, but we are already well beyond our nominal cutoff date and must desist from further discussion. In view of the uncertain future of the LMFBR, the subject of sodium-fuel aerosols may become of only academic interest. Even so, the fact that these changes in chemical constitution can cause differences in pharmacokinetics has a significant influence on health protection activities for this and other new technologies.

f. Transplutronics

While the behavior of elements such as americium was not neglected in the earlier years of research at Hanford, a more sustained effort concerning inhaled transplutronics occurred in the decade of the 1970s.

In 1973, the two plutoniums (-239 and -238) were compared to $^{244}\text{CmOx}$ in rats. Fresh $^{244}\text{CmOx}$ (calcined at 750°C) was highly soluble in lung with correspondingly higher depositions in liver and bone than plutonium. Survival time

(a) Evidently I was misled by personal observation of the blissful expression on the dogs' faces and comments from the operators into thinking all the beagles enjoyed their smokes (see chapter 3).

of the animals was shortest for curium. In fact, it was so short that there was not time for development of pulmonary metaplasia or neoplasia (Sanders, Craig, and Smith 1974; Sanders 1974).

In the same year, work on inhaled and intravenously instilled ^{253}Es was described in rats (Ballou 1974; Ballou, Busch, and Dagle 1974). Three forms were used, and intratracheal instillation was resorted to for part of the work because of the limited quantity of einsteinium available. The two routes were comparable except for the hydroxide. Radiation pneumonitis predominated at the highest dose, osteosarcomas at the intermediate dosages, and soft tissue tumors, including lung tumors, at the lowest dose. More pathologic observations came along in the next year. These indicated some bone tumors and fewer lung tumors for ^{253}Es compared to ^{239}Pu . The researchers speculated that einsteinium was even more a surface seeker in bone than plutonium.

By 1978 (Ballou et al. 1979), there had been time to follow late effects after inhalation. The high incidence of bone tumors and relatively fewer number of lung tumors seen after intratracheal instillation were not seen in the work with inhaled $^{253}\text{Es}(\text{NO}_3)_3$. This was puzzling because the calculated radiation dose to the lungs was higher after instillation, yet the incidence of lung tumors was higher after inhalation. The authors argue that the inhaled einsteinium is more uniformly distributed after inhalation and irradiates more sensitive tissue. Furthermore, those rats receiving high skeletal doses after inhalation also had severe lung damage, which resulted in early death due to radiation pneumonitis.

Exposures were made to study the carcinogenic effect of high-fired $^{241}\text{AmO}_2$ in rats. Lung clearance was rapid, as it was with cerium. At most, only lung and liver tumors have been seen. Despite its mobility, $^{241}\text{AmO}_2$, in this study at least, seems to be ineffective as a producer of bone tumors. By contrast, $^{241}\text{Am}(\text{NO}_3)_3$ is very rapidly removed from the lungs and is conspicuously effective in producing bone tumors.^(a) Furthermore, the calculated radiation doses to bone were only one-half those to the lung. This work seemed to need extension and confirmation. It got it in the next year, and it appeared that the special effectiveness was in the animals receiving 100 to 1,000 rad. In general, ^{241}Am seemed no more effective than plutonium or einsteinium in producing lung and bone tumors after inhalation.

Very recently, inhalation work with americium has been extended to the dog. This work includes a number of serum chemistry parameters. It should provide a useful contrast to the americium work at Utah using intravenous injection.

g. Thorium-Cycle Nuclides

In the chapter on uranium, and again in chapter 8, we bemoaned the lack of interest in radionuclides specific to a potential thorium fuel cycle. Following an essentially silent period after the war, except for tracer applications of the shorter-lived uranium isotopes, several laboratories have begun serious efforts to fill in the gaps by studying those radioisotopes more or less unique to the thorium fuel cycle. Inhalation work with some of these has been taken up in a modest way by Battelle at PNL. It can be seen in the 1979 annual report in work by Ballou and colleagues (Ballou, Gies, and Case 1980; Ballou, Gies, and Beasley 1980) on $^{232}\text{UO}_2(\text{NO}_3)_2$ and $^{233}\text{UO}_2(\text{NO}_3)_2$ and comparative toxicology of inhaled

(a) Usually differences in the type of compound of a radioisotope do not produce such a striking contrast in effectiveness. This is more like chemical than radiation toxicology.

actinide nitrates. The two uranium isotopes, despite some possible differences in pharmacokinetics (which, if real, may be related to factors other than isotope differences, e.g., the development of daughter products of ^{232}U), appear to have roughly comparable toxicity after inhalation. Both go primarily to skeleton.

The authors comment in the second paper that no "unusual toxicity" was found to be associated with inhalation of high-specific-activity isotopes of uranium in comparison to other actinide nitrates. This is not surprising since it is clear that uranium, while it moves to bone quite readily, is a volume rather than a surface seeker. Thus, any possible increase in bone tumorigenesis by virtue of greater translocation to bone may be modified by the site of deposition. A careful analysis is made of the possible reasons for the differences.

Later work tried intratracheal instillation of a solution of ^{232}U in equilibrium with its daughter products (^{228}Th , ^{224}Ra , ^{212}Bi , and ^{208}Tl). To do this, simultaneous measurements had to be made on several tissues by having three germanium detectors operating together. As seen in similar work using other routes of entry, the tissue distributions were decidedly not those of an equilibrium mixture. The details of nonequilibrium were different after inhalation from those after other routes of administration. This was reported by Ballou and his colleagues in 1981.

Also, ^{231}Pa , a major long-lived waste product of the thorium cycle, was introduced. This work is continuing.

h. Aerosol Science

Earlier in this chapter we reviewed briefly the development of aerosol science in the various laboratories. We noted that Hanford did not in general separate out aerosol work as a distinct entity. In this final decade of our consideration, both specific papers and groupings of summaries of aerosol work at this laboratory have appeared. These have considered the usual problems of relationship between size distribution, concentrations, and behavior; deposition, particularly alveolar deposition, as a function of both respiratory and aerosol parameters (see papers by D. K. Craig et al. in reports from 1971 through 1974) and some fairly elaborate methodology for determining respiratory parameters and their importance to deposition in various portions of the respiratory tract. Craig et al. (1972) obtained complete respiration data on ninety-eight dogs during the period of training and used these to compare with similar parameters obtained during exposure. Thus, predictions can be made for relatively short exposure periods. This work correlates closely with a remote control and measuring system developed at Rochester, which we will consider presently.

A final^(a) note on contributions of the aerosol group to the pulmonary radiotoxicology unit is seen in figure 9.22A and B. This represents what must be the ultimate in nose-only exposure chambers built to prevent rebreathing (Cannon, Blanton, and McDonald 1983, Cannon et al. 1982).

In figure 9.22A, the conventional method is diagrammed. In figure 9.22B, we see how separation of incoming and outgoing airstreams can be accomplished. This makes the rat nose-only exposure system more comparable to the mask and valve array used for the dogs.

(a) Except for the fact that they were drafted into characterization of Mount St. Helens volcanic ash. It was nearly inert compared to quartz particles.

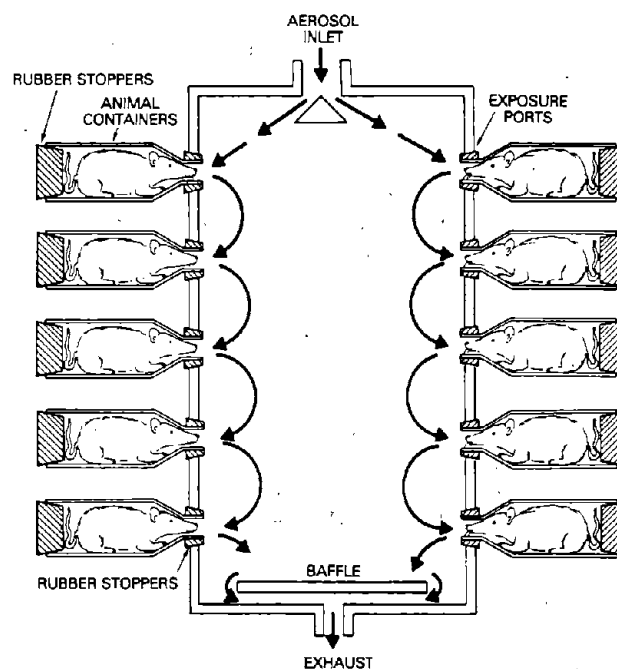


FIGURE 9.22A. Standard rat exposure chamber. (From Cannon et al. 1982.)

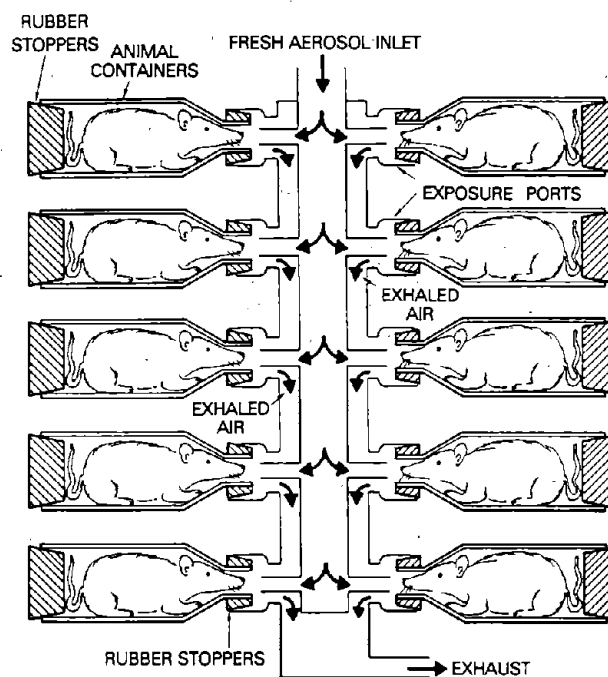


FIGURE 9.22B. New design for rat exposure chamber that avoids rebreathing aerosol. (From Cannon et al. 1982.)

i. Basic Overtones

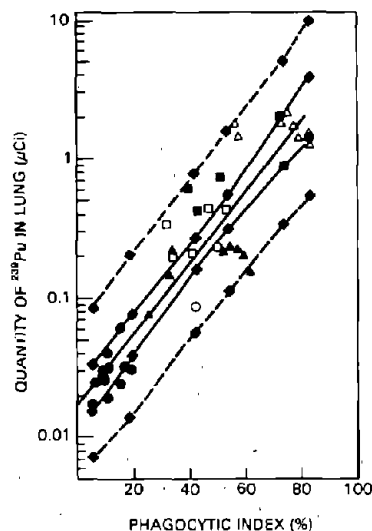
As we have seen, most laboratories with large long-term experiments under way did much work simultaneously on mechanisms. In the inhalation program at Hanford, a steady effort was maintained in several quarters. Chief among these was work on cellular interactions of plutonium carried out by Charles L. Sanders and collaborators. We will consider this work briefly in this final section. It extends over a considerable period.

Much interest attaches to the interactions between plutonium and the cells and tissues it comes in contact with. Biochemical phenomena have been observed in some depth (Taylor 1973a), and details of interactions with the cells of bone and bone marrow have been examined all over the world. It appears, however, that much less time has been devoted to these basic phenomena for inhaled radionuclides. For many years, only two names came readily to mind for work concerning the response of cells to an inhaled plutonium dioxide particle, Louis J. Casarett at the University of Rochester and Charles Sanders (a Rochester graduate) at Battelle. On the theory that the macrophages would be the cells most involved in such interactions, Sanders began with the peritoneal macrophage of the rat (Sanders 1969a). After perfecting techniques, the work was shifted to pulmonary macrophages (Sanders 1969b) and the gradual working out of the sequence of events. The plutonium was deposited in the peritoneal cavity or lung, which was then washed with sterile saline,^(a) and, thus, the plutonium was deposited in the peritoneal macrophage (Sanders 1969a). The time of application of the wash was varied in different experiments to provide both composite and serial pictures. The cells were washed and separated from other materials and prepared for light or electron microscopy, autoradiography, counting by DNA assay, and other treatments.

There was no doubt that plutonium particles were rapidly phagocytized by both peritoneal and alveolar phagocytes. By two hours after emplacement, over 90% of the plutonium particles had been phagocytized in the peritoneal cavity. The alveolar macrophages worked a bit more slowly, not reaching the approximately 90% level until after a day or more of contact.

The relation of quantity of plutonium in the lung and the phagocytic index (percentage of macrophages that had engulfed particles) is shown in figure 9.23.

FIGURE 9.23. Correlation between phagocytic index and log of amount of plutonium present in rat lung. (Samples obtained from 1 hour to 25 days after exposure. Correlation coefficient is 0.91. Outer solid lines represent 95% confidence intervals around regression line and outer dashed lines represent 95% confidence intervals for individual samples.) (Redrawn from Sanders via Bair 1970.)



(a) The washing process in lung gave many leads toward possible therapy, which we will take up in chapter 19.

Using a rather elegant technique of electron microscopic autoradiography, to which Sanders contributed importantly, as well as light microscopy combined with autoradiography, it was possible to observe details of the intracellular localization of plutonium within pulmonary macrophages. It is concentrated in the phagosomes of these cells. Frequently, quite striking amounts of plutonium would be accumulated within macrophages, e.g., a 500-fold concentration by peritoneal macrophages compared to the initial concentration in the peritoneal cavity. Indeed, accumulations were sometimes enough to interfere with preparation of thin sections by refusing to be cut through.

Such high concentrations of alpha radiation exacted a toll of the engulfing cells. Various stages of cytotoxic changes were seen developing, going into eventual cell disintegration. However, other macrophages came along to engulf both the plutonium and the cell debris, and the process was thus continued. In fact, it is not possible to tell in many cases whether the concentration seen in a given cell represents its own work or the engulfment of material already concentrated by previous phagocytic processes. However, it appeared that a single macrophage could retain plutonium particles for many months, thus accumulating a very large radiation dose.^(a)

The amount of plutonium in the alveoli influenced the amount found in macrophages, as shown in table 9.9.

TABLE 9.9. Influence of the Amount of Alveolar $^{239}\text{PuO}_2$ on the Concentration of PuO_2 in Alveolar Macrophages. Alveolar macrophages were removed from rat lung at 1-15 days after inhalation of PuO_2 by one 12 ml saline washing. Autoradiograms of macrophages on cytosmeareds were exposed for 14 days. Only alpha tracks passing outside the cell were counted.

\propto Tracks per Macrophage	Mean distribution in each class (%)		
	Mean Amount of ^{239}Pu in Lung (μCi)		
	0.03	0.4	1.7
2-5	51.3	18.5	8.2
6-30	39.8	36.1	25.4
>30	8.9	45.4	66.2

Source: Reset from Sanders 1972. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1972.

The retention half-time for PuO_2 in lung macrophages also varied with plutonium concentration (Sanders 1972). For example, with a mean lung burden of $1.7 \mu\text{Ci/g}$ lung, the retention time was about three days; with $0.06 \mu\text{Ci/g}$ mean lung burden, the retention time was over thirty days. This may reflect the killing of cells by the higher radiation doses. Sanders has also worked out intracellular particle size distributions and, thus, distribution of cellular dose, which is illustrated in table 9.10 taken from Sanders's work.

Obviously, the macrophages were transported by the lymph stream or transplanted themselves to areas such as pulmonary lymph nodes. It appears that

(a) Thus placing them among the most radioresistant of cells.

TABLE 9.10. Distribution of ^{239}Pu Activity Amongst Particles of Various Sizes Within Alveolar Macrophages Obtained by Saline Washings at 1-34 Days After Inhalation of $^{239}\text{PuO}_2$ by Rats. The amount of plutonium in 800 macrophages was autoradiographically determined in 8 exposed rats.

Fraction of $^{239}\text{PuO}_2$ -Laden Macrophages (%)	Equivalent* Particle Diameter (μm)	Amount of ^{239}Pu in Particle (μCi)	Fraction of Macrophage Plutonium in Each Size Class (%)	Radiation Dose† to Macrophage (rad/hr)
50	0.12	5.8×10^{-10}	2.5	0.5
24	0.16	1.4×10^{-9}	2.9	1.2
10	0.18	2.0×10^{-9}	1.7	1.8
4	0.20	2.9×10^{-9}	1.0	2.4
4	0.22	3.6×10^{-9}	1.2	3.2
4	0.26	6.0×10^{-9}	2.0	5.3
2	0.33	1.3×10^{-8}	2.3	11.0
2	>0.36	$>1.8 \times 10^{-8}$	86.4	>15.0

*Equivalent particle diameter = $0.0388 \left(\frac{\text{alpha track counts}}{\text{sensitivity (0.13)}} \right)^{1/3}$

†Assuming macrophage with diameter of $12.7 \mu\text{m}$.

Source: Reset from Sanders 1972. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1972.

most of the plutonium (and probably most of the majority of other heavy metals) concentrated in lymph nodes arrived in a macrophage. The basis for this conclusion is the fact that particles that were not phagocytized were rapidly cleared from the lung, and lung clearance after the first few days (in the rat at least) is almost all by or in pulmonary macrophages. *Thus, kinetics of movement of plutonium depends on macrophage kinetics.*

Sanders believes his findings explain the long retention time of plutonium in lung (Sanders 1972). The steps are immobilization of plutonium-laden macrophages in the alveoli, rapid engulfment by the alveolar epithelium, transport to the lymphatics, and sequestration in fibrotic zones of pulmonary tissue.

A final step (for purposes of this review) is the tracing of plutonium dioxide in the lung from macrophage to carcinoma. In an intriguing but somewhat complex discussion at a 1977 Hanford biology symposium^(a), Sanders et al. (1977) traced quantitatively the movement of plutonium in rat lung and the accompanying radiation dose. Despite the movement of macrophages, 80% of the energy absorbed is calculated to be delivered to alveolar septa. Of this 80%, only 10% each is absorbed by alveolar epithelium, macrophages, and endothelium, while 70% is absorbed by other elements present. Alveolar epithelium is an important target tissue, but neither it nor bronchiolar epithelium receives more than a small fraction of the total dose. When it is considered that a total dose of 78 rad delivered to *whole lung* of the rat over a period of about six hundred days produces a significant incidence of pulmonary adenocarcinoma,

(a) A glance at the table of contents of this symposium is enough to convince anyone that basic processes in the lung were not being neglected.

and the total energy calculated to be delivered to Type II alveolar epithelium or bronchial epithelium may be a small percentage of this, it is natural to ask if these very small amounts of energy can really cause the changes needed to produce a neoplasm. Is it due to the concentrated dose (which is, of course, much higher than the average dose) from the macrophages? Or is it due to a high early dose rate? To some other reason? Is there some mistake? The histological signs were largely negative at such doses. Also, why do adenocarcinomas predominate at low radiation doses, while squamous cell carcinomas are more characteristic of higher doses? The work at Hanford has made a start on these questions. We will have occasion to return to some of these problems when we look at the "hot particle" problem in lung.

A natural extension of the above work was to study the interaction with radioactive materials of phagocytic cells in in-vitro cultures, which Schneider and Robinson (1978) did in 1977. They could conclude, using two forms of plutonium and $^{241}\text{AmO}_2$, that the cellular effects seen are truly radiation, not chemical toxicity effects.

This work with macrophages is, of course, only an example of the basic overtones that accompanied the Battelle program. Since these were excellent scientists, they always looked for clues as to mechanisms. The histopathology reports are especially indicative of such interests and the generation of new information pertinent to mechanisms. Other areas were biochemical changes in lung, pharmacokinetic explanations for the differences in lung tumor response among species, pulmonary function evaluations, and others.

There is not room in these pages to follow these ideas in depth for each installation since both the basic problems and the attacks were similar in many laboratories. The easiest way to follow these is through the review papers, which sum up ideas developed over considerable periods. Many of those from Hanford have already been cited. Others that concentrate on pulmonary radiotoxicology are Bair et al. (1973); Dagle, Lund, and Park (1976); and Park et al. (1970). There was also work on biochemical mechanisms in the lung carried out by Tombropoulos et al. (1977), among others.

Comment: During the last decade that we have been reviewing, the Battelle people (along with others) expanded and diversified into other energy technologies, first under ERDA and then under the DOE. Much of the new work involved inhalation experiments. The superposition of these new enterprises put a real strain on both facilities and personnel; for it was unthinkable to give up the investment in the long-term studies and the unique expertise of the laboratory. Fortunately, the problems are not really very different, only the techniques. It is to the group's credit that they accommodated well and seemed to be able to attack the new without losing the essence of the old.

B. Lovelace Foundation—Inhalation Toxicology Research Institute^(a)

The Lovelace Foundation project was the last of the "king-sized" postwar experiments in internal emitter toxicology (chapter 8). It was the only one devoted exclusively to pulmonary radiotoxicology. It began as the "Fission Product Inhalation Laboratory" of the Lovelace Foundation and kept this name for many

(a) I have leaned heavily in preparing this narrative on an informal summary kindly provided me by the Institute's Director, Dr. Roger McClellan (1981).

years. As its mission and that of the host institution expanded, it was renamed "The Inhalation Toxicology Research Institute" (ITRI), the name it still bears.

1. Concept and Organization: Initial Activities

During the 1950s, the mounting concern for the effects of the radionuclides in fallout from the weapons testing program stimulated many new experimental efforts.^(a) The demands of the Aircraft Nuclear Propulsion (ANP) project, along with reactor safety considerations, added to the perceived needs. Despite the active programs at Utah and Davis, which concerned intravenous and oral routes of administration, and the inhalation work at Hanford, a major program devoted to the *inhalation of fission products* was considered essential.

As we saw in chapter 8, the capabilities of existing laboratories were always considered first before initiating a new project. The prime candidate was Rochester. However, the size of the program planned made the Rochester location on a relatively compact campus in the northeastern climate undesirable. Furthermore, Rochester was already involved in the long-term uranium experiment and in other research in pulmonary radiotoxicology and aerosol science. Full commitments to other programs or problems of space for expansion dissuaded the planners from other locations also. These included Hanford, Davis, and the Argonne National Laboratory.

There then occurred one of those happy coincidences that influence the development of science as well as other facets of human activity. The Lovelace Foundation for Medical Education and Research, which started as a largely clinically oriented group in Albuquerque, New Mexico, had developed during the early and mid-1950s strong activities in aviation medicine and pulmonary physiology. As a part of this, they had engaged in research on the biological effects of blast, initially for AEC, later for the Department of Defense (DoD). The facility for this work was located on an outlying area of Sandia Base, a few miles from the Lovelace Clinic, which was itself on the edge of the desert base. The blast biology work was winding down. W. Randolph Lovelace, Jr., son of the founder of the clinic, evinced interest in some new work. Dr. H. D. Bruner, who had major responsibilities at AEC Headquarters for the administration of the pulmonary radiotoxicology work (Bruner 1979), learned of the interests at Lovelace. Headquarters staff already knew the clinic's other work in respiratory physiology. Thus, in June 1959 the Division of Biology and Medicine of AEC contacted Dr. Clayton S. (Sam) White, who was then Director of Research for the Lovelace Foundation and who had managed the blast biology program, relative to taking on a project on the effects of inhaled fission product radionuclides. They were interested, and a plan was submitted in January 1960. By June 1960, a contract was awarded. On the Lovelace side were Dr. White and W. R. Lovelace, Jr. (Randy). On the AEC side were Dr. Bruner and, backing him both scientifically and administratively, Dr. C. W. Shilling, deputy director of the Division of Biology and Medicine.^(b) The nearness to Sandia Base and Kirtland Air Force Base was a plus because of the presence there of many radiation physicists and chemists.

(a) We will review the broad picture of such research in chapter 13.

(b) It was my privilege to visit Randy Lovelace and Sam White in Albuquerque in company with Dr. Shilling and to be present at part of the "keel laying" activities for this important new enterprise. Dr. Shilling is a retired Navy Captain, so the keel laying analogy comes naturally.

There were no formal "Founding Fathers" for this project. There was considerable information and planning exchange with other laboratories doing inhalation work. This was accomplished partly through the AEC Headquarters staff, particularly Dr. William Lotz, who had assumed some of the administrative work for the internal emitter research with H. D. Bruner. A group called the "Inhalation Toxicology Working Group" met rather frequently at the cognizant laboratories. There were representatives from each of the major inhalation programs in this group. There was also a small advisory committee to assist Drs. Bruner and Lotz. Some meetings of the latter group placed special emphasis on the developing plans of the Lovelace experiments and were held at Albuquerque.

Randy Lovelace placed Sam White in charge of developing facilities and assembling staff. The remainder of 1960 was spent on these plans, plus the preliminary design of experiments.

In January 1961, T. T. (Tom) Mercer, whom we met in the section on aerosol science, arrived at Lovelace with a Ph.D. from Rochester and experience in England, at the Naval Radiological Defense Laboratory, and the University of Washington. He set to work immediately on the research required to produce and characterize the radioactive aerosols needed. The aerosol physics section, which he started, has been a powerful and productive one ever since.

In February 1961, Robert G. (Bob) Thomas arrived from Rochester to establish a radiobiology section. He laid plans fairly soon to have the respiratory parameters measured and recorded on *each and every animal exposed*, small or large.

The reason for this decision deserves attention. Over the years, inhalation exposures had characteristically involved either placing animals in a chamber whose ambient air contained the substance of interest or arranging the "nose-only" procedure, where only the tip of the animal's snout protruded into the aerosol stream. With the former method, there are always questions regarding intake by licking the fur and the uniformity of distribution of the material in the chamber. With the nose-only method, the contamination of fur is eliminated, but it is still necessary to estimate intake by calculation from the exposure concentration. As we have already seen, special equipment has been designed and used at Hanford and Rochester to measure deposition as well as many other respiratory parameters directly. But the Lovelace idea of measuring tidal volume, ventilation rate, etc., for each individual animal was a new and somewhat heroic development. The result, a knowledge of how much each animal took in, was considered worth the effort. A bit further along we will see how it was managed.

By the end of February 1961, White, Mercer, and Thomas submitted plans for a facility and a program. In less than two weeks, the plan had informal approval with instructions to develop initial experiments and to complete the building plans.^(a) By June, a contract was let for design and construction of a facility on the southern part of Sandia Base to accommodate work that had to be somewhat isolated.

A unique facility was planned which, among other things, utilized the abundant evaporative potential of the desert climate to greatly reduce the volume of liquid waste requiring disposal by the use of open holding ponds. Good separation of "hot" and "cold" operations was facilitated by the abundance of land to spread out upon. A purebred beagle dog colony was begun in 1961 using dogs

(a) Such timing is more like the Manhattan District days than current bureaucracy. It attests to the confidence the people and plans commanded at AEC Headquarters.

from some of the other large AEC projects and also commercial breeders and experience gained in the already existing colony at Hanford. The details of development and the care and breeding of this colony have been given by Redman et al. (1970). Redman joined the staff in September 1961.^(a) The interim facilities for the dog colony and for some of the experimental work were ready by late summer 1961.

In June 1961, Ms. Randi Lie (later to be Mrs. Robert Thomas) joined the staff with an M.S. degree from Rochester. In December 1961, Dr. Bruce Boecker with a Ph.D. from Rochester and experience with field release studies of fission products while a graduate student (see chapter 14) joined the group. Experimental work began in the Headquarters facilities of Lovelace Foundation.

Bruce Boecker and Bob Thomas worked in parallel on developing apparatus and protocols for exposure of small rodents (Thomas) and dogs (Boecker), while Mercer worked on the aerosol generation problems as well as basic aerosol science.

Following the plan that each animal should have its respiratory parameters measured during exposure, plethysmographs of varying size and design were created and tested. Some of the early ones for rats, along with old and new exposure chamber designs, were described by Thomas and Lie (1963) in a moderately early "LF" report. This report includes also the full procedural protocol for the small-animal work.

A diagram of this exposure assembly is shown in figure 9.24. Note that a body plethysmograph was attached to each of the several openings in the chamber.

The corresponding development for dogs was described by Boecker, Aguilar, and Mercer (1964) at the Hanford symposium on Inhaled Particles and Gases. Because it was desired to keep animal movements from becoming extreme and thus interfering with the plethysmograph record, the dogs were placed in a sling, which was in turn placed in the chamber-plethysmograph. In order to isolate the system from the room air and prevent changes in room air pressure (e.g., door opening) from causing wide fluctuations in the pneumotachograph base line, a compensatory chamber was arranged atop the exposure chamber-plethysmograph. The pressure changes were, of course, sensed by transducers and recorded.

The reading of separate plethysmograph records for each animal was a most laborious and time-consuming process. It was not long before an automated system was designed and put into operation (Goodrich and Thomas 1963).

While this work was in progress, some of the biomedical personnel in the Foundation in fields like biochemistry, microbiology, and pathology were oriented into the program for studies of radiation effects. Dr. Robert K. Jones, an M.D. pathologist from the University of Cincinnati with Air Force experience, joined the group in August 1964. He joined Dr. James Scott from Rochester and the University of Virginia who came in 1962 as the second full-time pathologist to the program. Others were Dr. T. Chiffelle, pathology; Dr. B. Longwell, biochemistry; and Dr. W. Clapper, microbiology. These portions of the program were accommodated in a major expansion of the Lovelace Headquarters facilities begun in 1962.

(a) Dr. H. C. Redman graduated from the University of California at Davis in Veterinary Medicine. He had experience while a student working at the Nevada Test Site (UCLA Project) and service in the Air Force at the Radiobiology Laboratory at Kirtland Base in Albuquerque.

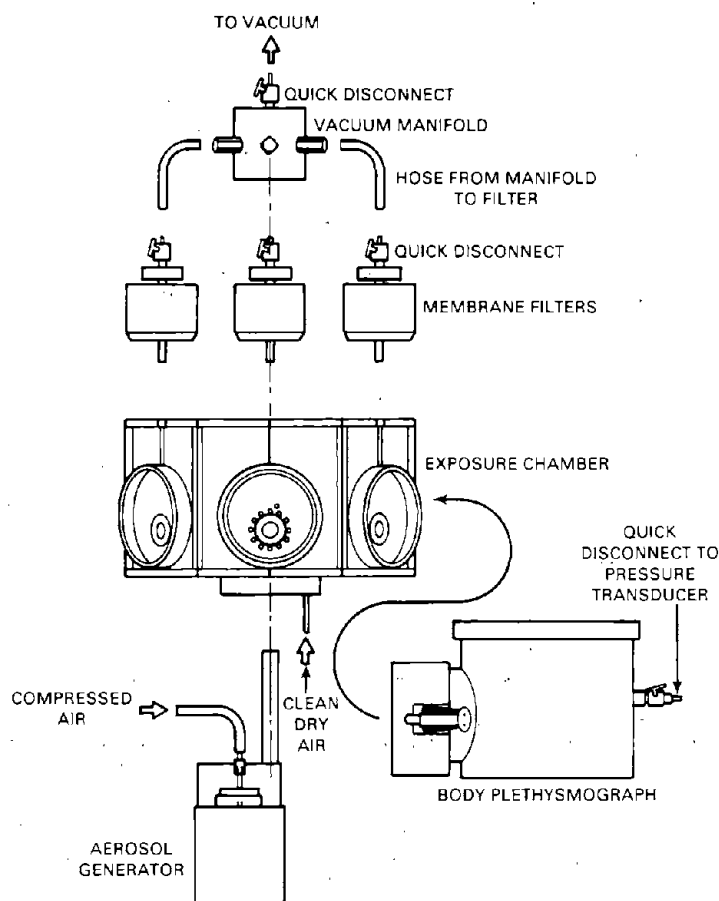


FIGURE 9.24. Early Lovelace exposure assembly for small animals. (Redrawn from Thomas and Lie 1963.)

It was decided early that the complexities of handling and exposing animals to mixed fission products posed undesirable problems. Therefore, much of the early work utilized ^{137}Cs . Because of pressures from the field problems, some effort went also into the burning of fuel elements, but this never reached the stage of exposing animals at Lovelace.

The earliest "LF" reports and publications related to aerosol science and the development of equipment. A string of reports and publications by T. T. Mercer concerning primarily the cascade impactor resulted from work during this early period. A sampling of these is Mercer, Tillery, and Ballew (1962); Mercer (1963, 1964, 1965). An excellent overview of these and other developments is given by Raabe (1970 and 1972), and we thus can refrain from further detail here.

Later developments in aerosol science were the decision to use stable cesium chloride as a common vector for the "soluble" aerosols and the development of

a standardized "insoluble" carrier, fused montmorillonite clay particles.^(a) The technique for the former was to add the radionuclide of interest to a cesium chloride solution. (Controls of cesium chloride alone were always run.) For the insoluble vector, the radionuclide of interest was attached to montmorillonite clay by ion exchange, an aerosol of labeled clay particles generated and treated at high temperatures to fuse the particles into a relatively insoluble form. Thus, the aerosols used for the main thrust of the Lovelace program were different from those used at Hanford, Rochester, and elsewhere. The theory was that particle size and solubility, being properties of the vector, would be more constant and controllable than they were with aerosols made up idiosyncratically for each radionuclide. The advantages are numerous if dosage pattern is to be controlled reproducibly, and this was the intent of the Lovelace experimenters. There are disadvantages too. Perhaps the primary one is that behavior of the administered radionuclide may be submerged in behavior of the carrier particles. However, experiments at other laboratories were checking on these points. Also, some sort of vector is present for most radioactive aerosols, and there are advantages in having only two vectors, one for soluble aerosols and one for insoluble.^(b)

Only a few results beyond aerosol techniques and laboratory and experimental plans will be considered in reviewing this initial phase of the Lovelace work.

Thomas (1964b)^(c) developed theoretical functions for predicting the concentration of materials in lung and lymph nodes following inhalation and compared them to experimental studies from a number of laboratories, including Lovelace. Lie (1964) published some of the early work in rats with ^{137}Cs inhaled in two forms, chloride and nitrate. Greater amounts were deposited at the larger particle sizes. Retention kinetics seemed not to be influenced by the particle sizes inhaled. This result is somewhat contrary to experience with uranium and in other laboratories with other materials. It may or may not be actually different. The particle-size range was not large, about $0.3\ \mu$ to $1.9\ \mu$ "equivalent diameter" (standard deviation not given), but in the range of the other experiments. It cannot be determined whether this reflects behavior of cesium or the fact that the experimental technique allowed determination of actual deposition in each animal. Also, concentration (i.e., initial deposition) in lung, kidney, and liver was greater at smaller particle sizes, consonant with other work.

2. The Major Programs Begin

Even though the period 1960 to 1964 was far from inactive, the emplacement of large, in contrast to range-finding, experiments had to await the completion of facilities on the Sandia Base safe for handling aerosols with penetrating radiation and the presence of adequate senior and supporting staff.

In October 1963, there was a program review of the Lovelace project in conjunction with a meeting of the AEC Inhalation Toxicity Group. There was general agreement to continue the work with several animal species and to have as balanced a program as possible. Because of the complexities of a dog program, emphasis was placed on getting started with exposure of the beagles.

(a) A hydrous aluminum silicate found at Montmorillon, France. This will be abbreviated to "FAP"—"fused aluminosilicate particles"—in subsequent discussions.

(b) This general plan was later expanded for the long-term experiments (see next section).

(c) This paper was widely circulated, and versions appeared also in proceedings of the IAEA and the Bioassay Group.

The first dog was exposed to a radioactive aerosol in the permanent Lovelace facilities on January 29, 1964. This followed up the work with rats and used a ^{137}Cs chloride aerosol. There thus began a major program that is still in progress. For many years it stuck closely to the original charge, viz., to study the pulmonary radiotoxicology of the biologically important fission products. Despite the work we have already seen from the World-War-II years and individual experiments elsewhere, this was the first major coordinated long-term study of fission products by the inhalation route in a large animal.

In addition to ^{137}Cs , Lovelace added ^{91}Y , ^{144}Ce , and ^{90}Sr , all as chlorides and thus a relatively soluble form. The development of the technique for preparing fused montmorillonite clay as a carrier added the potential dimension of an insoluble form for all of these radioisotopes. Strontium-90 titanate was also used as a relatively insoluble form of this element. The FAP experiments included $^{90,91}\text{Y}$, ^{144}Ce , and ^{90}Sr . The exposures began with young adult beagles, thirteen months of age. Gradually, experiments were added with $^{144}\text{CeO}_2$ using Syrian hamsters of different ages; ^{90}Y FAP, $^{144}\text{CeO}_2$, and ^{141}Ce FAP in mice; and $^{144}\text{CeO}_2$ in rats. We will save discussion of the long-term results for a consolidated look in a later section.

This period was not all uninterrupted progress. In summer 1965, Tom Mercer left Lovelace to go back to Rochester to head up their basic aerosol program. As we saw in the section of this chapter on aerosol science, Bob Thomas filled in the gap in addition to his other work. Otto Raabe arrived near the end of 1966, and George Kanapilly came in 1967. Fortunately, the basic aerosol techniques had been worked out by Mercer with Thomas helping to apply them to the animal chambers. Thus, the hiatus in aerosol science did not delay the exposures. The new arrivals had different basic interests, which we will see presently.

Also in 1965, the AEC Division of Biology and Medicine sponsored another review of the Lovelace activities. At this meeting, Dr. H. D. Bruner's growing concern that not enough attention was being devoted to studies with dogs was aired. The original Lovelace design to have many species and much probing done with short-lived species still made scientific sense, but Headquarters seemed to have difficulty financing broad programs at several places and considered the Lovelace program as a "dog program" like Utah and Davis. After the meeting, the Foundation was directed to shift major emphasis to life-span studies with beagles.

In December 1965, W. R. Lovelace II was killed in a private airplane crash in the Colorado Rockies. Changes in the Foundation's leadership had to follow. Clayton White became president of the Lovelace Foundation and decided he could no longer manage the fission product research program. Through a series of fortunate coincidences, Dr. Roger O. McClellan was finishing up a tour of duty at AEC Headquarters, where he had been on leave from the Hanford Biology Operation. He had experience with radioisotope problems dating to summer work at Hanford in 1957, 1958, and 1959; a degree in veterinary medicine from Washington State University; and subsequent experience with internal emitter research at Hanford and on his assignment to Headquarters. On September 12, 1966, Roger McClellan became director of the Fission Product Inhalation Program at Lovelace. The program has prospered ever since.

One of Dr. McClellan's first actions was to push completion of the exposure of the dogs according to plan. He also began adding some needed professional personnel, e.g., Antone L. Brooks, a recent Cornell graduate in cytogenetics.

The exposures to ^{90}Sr chloride, ^{144}Ce chloride, and ^{91}Y chloride were well under way in late 1977 when the Foundation sponsored a meeting (the first) of its own review panel. The original plan of exposing groups of dogs to both soluble and insoluble forms of many different elements and using at least three exposure levels had begun to look overwhelming, if not quite impractical. At this meeting, one of the reviewers, Dr. Roy Albert of NYU, suggested they employ the more or less standardized approach we have already mentioned, viz., use a common vector for different elements in a given category, i.e., cesium chloride for soluble forms and the FAP vector for the insoluble forms. This idea was adopted quickly. It meant that exposure techniques would not try to imitate "real-world" situations for each radionuclide. Instead, radiobiological information would be sought using the large differences in dose and dose-rate to lung and other organs uncomplicated by the idiosyncratic properties of aerosols involving each element. The exposure of young adult dogs to ^{90}Y , ^{91}Y , ^{144}Ce , and ^{90}Sr in fused aluminosilicate took place from 1968 to 1970.

3. Results of the Lovelace Inhalation Program with Beta- and Gamma-Emitting Radionuclides

a. Single Exposures

We will skip some years of interim developments in order to review without delay some of the results of the long-term effort.

A summary of the work with ^{90}Sr was presented by McClellan et al. (1972) at the AEC-sponsored symposium on Biological Implications of Radiostrontium held at Davis, California. They reported the same large differences due to form inhaled as we have noted from earlier work; but they could go a few steps further. The relatively soluble forms were rapidly absorbed from both lung and gastrointestinal tract and were distributed to tissues much as after oral or intravenous administration. Effects were also similar, viz., hematopoietic damage early at high doses and neoplasms of bone and contiguous tissues at later times. By contrast, the relatively insoluble form was retained for long periods in the lung with slow translocation to the skeleton and the tracheobronchial lymph nodes. At high doses, the insoluble forms caused radiation pneumonitis and pulmonary fibrosis. No lung tumors were seen at this stage, but some were predicted.

McClellan went to considerable lengths to compare the pharmacokinetics of the strontium chloride inhaled to the strontium citrate injected intravenously in the Utah work. The whole-body retention was larger by up to 40% initially after the *intravenous* injection. This difference gradually decreased so that the retention factors were identical after fifteen hundred days. The reasons for the more rapid loss after inhalation were attributed to the clearance from the respiratory tract to gut. Nevertheless, inhaled soluble strontium that reaches the lung is rapidly absorbed therefrom. Differences between the behavior of inhaled *insoluble* strontium and injected strontium in the Utah experiment were large and continuous.

Several completed studies in rats appeared in the early 1970s. These included a comparison of inhaled and injected iodine, the transferability of ^{90}Sr -induced leukemia in Holtzman rats, niobium and zirconium oxide distribution and excretion, effect of temperature on antimony aerosols, and short side experiments with dogs.

As the program evolved, there were eight major dog experiments with young adult beagles: four with relatively soluble forms ($^{90}\text{SrCl}_2$, $^{144}\text{CeCl}_3$, $^{91}\text{YCl}_3$, and

$^{137}\text{CsCl}$) and four with relatively insoluble forms (^{90}Y , ^{91}Y , ^{144}Ce , and ^{90}Sr , all as FAP). Two additional major experiments, added in 1972, exposed immature dogs (three months old) and old dogs (eight to ten years old) to ^{144}Ce FAP.^(a) Small-animal work with the same purposes ran in parallel.

In 1975, repeated exposures were added for comparison of both metabolism and effects with single exposures.

Each experiment had roughly the same format, viz., a large group of animals was exposed and set aside for life-span study, while a smaller group was entered into a serial-sacrifice program to determine distribution and excretion over the long pull and to watch the development of histopathology. There were, of course, autoradiographic studies and many special determinations, some on animals in the regular progression, others by special additions.

A broad summary of the distribution data, which could be used for dose-response calculations, is shown in table 9.11. While not the very latest, these results (1979) are near enough to the end of our period of coverage to give a broad view of the experiments (Hahn et al. 1979a).

TABLE 9.11. Dose-Response Longevity Studies—Beta Emitters, Lovelace Foundation

Radionuclide and Form	Whole-Body Retention Effective Half-Life	Age at Inhalation Exposure	Organs Receiving Substantial Radiation Doses				
			Lung	Skeleton	Liver	Whole- Body	TBLN
<i>Beagle Dogs</i>							
¹³⁷ CsCl	30 days	13 months				++	
⁹¹ YCl ₃	59 days	13 months	++	++	++		
¹⁴⁴ CeCl ₃	284 days	13 months	++	++	+++		
⁹⁰ SrCl ₂	5-10 years	13 months		+++			
⁹⁰ Y FAP	2.6 days	13 months	++				++
⁹¹ Y FAP	53 days	13 months	+++				+++
¹⁴⁴ Ce FAP	≈200 days	13 months	+++	+	+		+++
⁹⁰ Sr FAP	≈400 days	13 months	+++	+			+++
¹⁴⁴ Ce FAP	≈200 days	3 months	+++	+	+		+++
¹⁴⁴ Ce FAP	≈200 days	8-10 years	+++	+	+		+++
<i>Syrian Hamsters</i>							
¹⁴⁴ CeO ₂	≈63 days	28 days	+++	+	+		
¹⁴⁴ CeO ₂	≈63 days	84 days	+++	+	+		+++
¹⁴⁴ CeO ₂	≈63 days	340 days	+++	+	+		+++
<i>Mice</i>							
⁹⁰ Y FAP	≈2.6 days	6-8 weeks	++	+			++
¹⁴⁴ CeO ₂	≈21 days	8-10 weeks	+++	+	+		+++
¹⁴⁴ Ce FAP	≈21 days	15-20 weeks	+++	+	+		+++
<i>Rats</i>							
¹⁴⁴ CeO ₂	≈85 days	12 weeks	+++	+	+		+++

FAP = Fused aluminosilicate particles.

TBLN = Tracheobronchial lymph nodes.

+ = Relative magnitude of dose received.

* ^{144}Ce , ^{90}Sr and ^{137}Sr as used in this test refer to ^{144}Ce in equilibrium with its daughter, ^{144}Pr , ^{90}Sr in equilibrium with its daughter, ^{90}Y , and ^{137}Cs in equilibrium with its daughter, $^{137\text{m}}\text{Ba}$.

Source: Reset from Hahn et al. 1979a.

(a) Cerium-144 refers to ^{144}Ce in equilibrium with its daughter, ^{144}Pr ; ^{90}Sr refers to ^{90}Sr in equilibrium with its daughter, ^{90}Y ; and ^{137}Cs is in equilibrium with its daughter, $^{137\text{m}}\text{Ba}$.

The variations in whole-body retention time and the dose to important organs, dependent to a large extent on retention time also, can be seen in this table. Also apparent are the larger retention in whole body and larger dose to lung with the insoluble forms; the lack of accumulation in lymph nodes of the soluble forms; the greater dose to skeleton from the soluble forms of ^{91}Y , ^{144}Ce , and ^{90}Sr ; and the greater dose to liver from the soluble forms of ^{91}Y and ^{144}Ce . While the whole-body retention half-time was markedly lower for both immature and aged dogs receiving ^{144}Ce FAP, the organs receiving substantial radiation doses did not change.

The results with hamsters, rats, and mice confirmed in general the findings in dogs but did not always agree quantitatively among themselves (see Snipes, Boecker, and McClellan 1983).

An illustration of the marked difference in dosage pattern, including total accumulated doses for the different radionuclides, all in insoluble form, is seen in figure 9.25. Naturally, the initial dose rates to lung vary in more or less inverse fashion to the order shown in figure 9.25, and, as shown in figure 9.26, these differences in dose rate are very large indeed.

FIGURE 9.25. Absorbed beta dose rate to the lungs of beagle dogs from various inhaled radioactive aerosols normalized to an initial dose rate of 100 rads/day (110 g lung). Lovelace work. (Redrawn from Hahn et al. 1979a.)

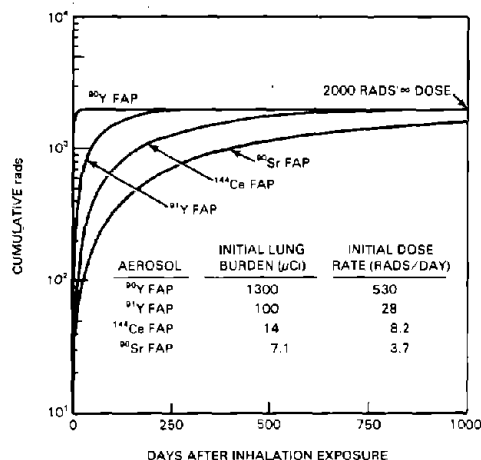
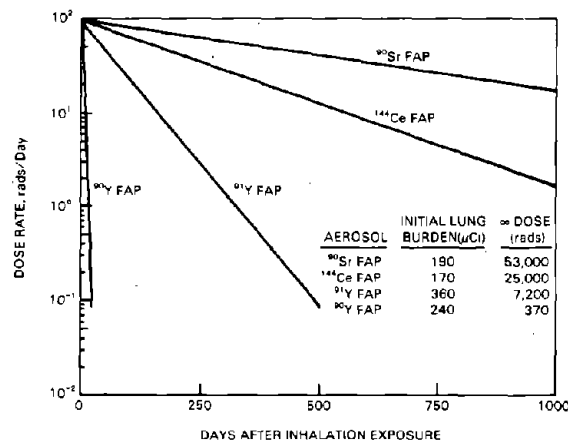


FIGURE 9.26 Patterns for accumulating 2000 rads total beta dose to the lungs of beagle dogs from various inhaled radioactive aerosols (110 g lung). Lovelace work. (Redrawn from Hahn et al. 1979a.)

A summary of the primary biological effects, the numbers of animals used, and other details of the eight life-span experiments in young adult dogs are given in table 9.12. Special mention should be made of the following:

1. Nasal cavity neoplasms were fairly common with the soluble compounds. Except for carcinomas of the nasal sinuses from radon, produced by radium in situ (chapter 1), such lesions are not common with inhaled alpha emitters. The greater penetrability of the beta particles may be the cause of the difference.
2. Soluble $^{144}\text{Ce Cl}_3$ caused neoplasms of nearly all tissues considered as potential targets. Liver problems were particularly notable with this isotope and form.
3. Only bone neoplasms appeared as a late effect of soluble strontium. Leukemia appeared in the one- to two-year period and bone marrow aplasia in the early period. Strontium seems to be different from the other elements tested.

TABLE 9.12. Observed Biological Effect in Longevity Studies of Beta Emitters Inhaled by Dogs (9/30/79)

Radio-nuclide and Form	Organ Receiving Major Radiation Dose	Number in Study (a)	Early Effects to 1 Year	Intermediate Effects 1 to 2 Years	Late Effects Over 2 Years	Current Age of Survivors (Years After Exposure)	Number Surviving
$^{137}\text{CsCl}$	Whole body	66	Marrow aplasia	—	Neoplasia—Miscellaneous organs	10.6-11.3	36
$^{91}\text{YCl}_3$	Skeleton Lung Liver	58	Marrow aplasia	—	Nasal cavity neoplasms Lung neoplasm	12.3-12.9	19
$^{144}\text{CeCl}_3$	Skeleton Liver Lung	72	Marrow aplasia Liver degeneration Radiation pneumonitis	Liver degeneration Pulmonary fibrosis	Liver neoplasms Bone neoplasms Nasal cavity neoplasms Leukemias Lung neoplasms Liver degeneration	12.0-13.7	13
$^{90}\text{SrCl}_2$	Skeleton	97	Marrow aplasia	Leukemia	Bone neoplasms	12.4-14.2	12
$^{90}\text{Y FAP}$	Lung	101	Pulmonary vasculitis Radiation pneumonitis Pulmonary fibrosis	Pulmonary fibrosis	Lung neoplasms	8.5-10.0	55
$^{91}\text{Y FAP}$	Lung	108	Pulmonary vasculitis Radiation pneumonitis Pulmonary fibrosis	Pulmonary fibrosis	Lung neoplasms Mediastinal neoplasms	8.0-9.5	47
$^{144}\text{Ce FAP}$	Lung	125	Pulmonary vasculitis Radiation pneumonitis Pulmonary fibrosis	Pulmonary fibrosis	Pulmonary fibrosis Lung neoplasms Bone neoplasms Liver neoplasms Nasal cavity neoplasms Mediastinal neoplasms	8.1-11.8	67
$^{90}\text{Sr FAP}$	Lung	124	Radiation pneumonitis Pulmonary fibrosis	Radiation pneumonitis Pulmonary fibrosis Lung neoplasms	Lung neoplasms Heart neoplasms Mediastinal neoplasms Nasal cavity neoplasms	4.8-9.7	49

FAP = fused aluminosilicate particles.

(a) Original states "number of study."

Source: Reset from Hahn et al. 1979a.

4. As seen in studies discussed earlier, pneumonitis and lung fibrosis were universal early effects of the insoluble forms.
5. Later effects of insoluble forms were limited to lung and adjacent tissues for ^{90}Y , ^{91}Y , and ^{90}Sr , except for heart neoplasms with ^{90}Sr . Bone and liver were involved along with the respiratory tract with ^{144}Ce .
6. Some lung tumors spawned osteosarcomas.
7. The protracted irradiation from ^{90}Sr and ^{144}Ce is relatively more efficient in producing pulmonary hemangiosarcomas than less protracted patterns.

An especially notable finding in this long series of experiments was the occurrence of tumors in the mediastinum and vessels of the tracheobronchial lymph nodes with insoluble ^{144}Ce . As described many times, the very large calculated radiation doses to the lymph nodes draining the lungs have suggested use of this tissue as a critical organ in establishing maximum permissible exposures for inhaled insoluble radionuclides. (See, for example, Myers 1972 and chapter 16.) While there was plenty of evidence of effects, including complete necrosis of the lymph nodes, cancer seemed never to arise in these areas. (A few instances of invasion by tumors originating in other areas are known.) For this reason, among others, lymph nodes were never designated as a critical organ (cf. Myers 1972).

In report number XII on the toxicity of inhaled insoluble ^{144}Ce , Hahn and colleagues (1979b) describe primary tumors (hemangiosarcomas) of the tracheobronchial lymph nodes (TBLN) of dogs. They were not the most frequent tumor; primary lung tumors were the most frequently observed. Nevertheless, this occurrence removes a puzzling discrepancy from past work since it seemed unlikely that the TBLN would *never* be the site of a primary tumor, as had seemed to be the case. A concise published version was presented at the Hanford life sciences symposium in October 1979 (Hahn and Boecker 1980). There can be no doubt that the tumors are real and primary. Details for those animals that showed these tumors, as a late effect, are given in table 9.13. Note the enormous calculated radiation dose to lymph nodes and the relatively large dose to lung also. But note also (table 9.12) that many other effects and neoplasms occurred in the fifty-nine animals that had died after exposure to insoluble ^{144}Ce . This is even more striking when the wide range of effects seen is

TABLE 9.13. Dosimetric and Pathologic Data for Dogs That Died With Tumors Arising from the Tracheobronchial Lymph Nodes After a Single Inhalation Exposure to a Relatively Insoluble Form of ^{144}Ce

Dog Number	ILB ($\mu\text{Ci/kg}$)	To Death			Primary Cause of Death	Metastasis of TBLN Tumor
		Cumulative Rads to TBLN	Cumulative Rads to Lung	Days After Exposure		
208D	15	130,000	20,000	2396	Tumor-Mediastinum	Yes
467A	13	110,000	17,000	1763	Tumor-Mediastinum	Yes
326C	12	100,000	16,000	3280	Tumor-Mediastinum	Yes
323V	7.8	68,000	10,000	2107	Tumor-Mediastinum	Yes
478B	5.7	50,000	7,500	2502	Tumor-Mediastinum	Yes
211F	19	170,000	25,000	3250	Tumor-Lung	No
455B	12	170,000	25,000	2179	Epilepsy	No

ILB = Initial Lung Burden.

Source: Reset from Hahn et al. 1979b.

reviewed, as in table 9.14. It appears that ^{144}Ce is the most indiscriminating of the radionuclides in the organs and tissues it chooses to affect.

Similar tables are shown in the annual reports for each experiment. Those for the soluble forms show some variety but less than that seen in table 9.14. The summaries for the insoluble substances tend toward more constancy of

TABLE 9.14. Summary of Deaths of Dogs Exposed by Inhalation to ^{144}Ce in Fused Aluminosilicate Particles (9/30/79)

Diagnosis	Number of Dogs	ILB's ($\mu\text{Ci/kg}$ Body Weight)	Survival Times (DPE)	Cumulative Dose to Lung (rads)
<i>Respiratory Tract</i>				
Radiation pneumonitis and pulmonary fibrosis	16	41-210	143-410	28,000-140,000
Pulmonary vasculitis	1	33	193	24,000
Pulmonary fibrosis and pulmonary thrombosis	1	32	1228	38,000
Pulmonary hemangiosarcoma	5	26-54	765-1526	29,000-59,000
Pulmonary hemangiosarcoma and fibrosarcoma	1	46	750	61,000
Pulmonary hemangiosarcoma and pulmonary adenocarcinomas	2	29;35	916;1226	43,000;44,000
Bronchioloalveolar carcinoma	1	27	1523	33,000
Bronchioloalveolar carcinoma, mixed tumor of lung	3	19-24	1810-3250	25,000-32,000
Bronchioloalveolar carcinoma hemangiosarcoma-primary site undetermined	1	34	2313	44,000
Squamous cell carcinoma, nasal cavity	1	24	1253	32,000
<i>Other Organs</i>				
Hemangiosarcoma, mediastinum ^a	6	2.4;13	1763-3749	3200-22,000
Hemangiosarcoma, bone	3	14-19	1974-2471	18,000-25,000
Hemangiosarcoma, liver	2	17;7.6	2327;2570	23,000;12,000
Hemangiosarcoma, spleen ^a	2	18;24	1895;2728	23,000;33,000
Hemangiosarcoma, heart ^a	2	10;12	1527;2849	13,000;15,000
Hemangiosarcoma, dermis	1	8.9	2365	13,000
Hemangiosarcoma, site undetermined ^a	2	4.9;5.4	1793;2753	6000;7,800
Transitional cell carcinoma bladder	1	0.44	2682	550
Accidental death ^a	2	0.02;13	1749;2612	29;18,000
Pleuritis, peritonitis (<i>Nocardia</i>)	2	1.8;12	2392;2502	2600;15,000
Epilepsy	1	19	2179	26,000
Lymphoma ^a	1	11	4179	16,000
Peripheral nerve tumor ^a	1	0.77	3578	110
Undetermined ^a	1	1.3	3574	2000

^aIncludes some dogs which have not had diagnosis verified histologically.

DPE = days postexposure

Source: Reset from Hahn et al. 1979b.

diagnosis at death or euthanasia. With soluble strontium, bone neoplasms outnumbered all others, while with $^{91}\text{YCl}_3$ and $^{144}\text{CeCl}_3$ hematologic dyscrasias predominated, followed closely by carcinoma of the nasal cavity with $^{144}\text{CeCl}_3$. Yet, the number of other dyscrasias and lesions was considerable.^(a) With ^{90}Y , in contrast to other insoluble substances, a predominance of one effect was marked, viz., thirty-eight of forty-six cases died from radiation pneumonitis and pulmonary fibrosis (due probably to the high dose rate delivered by ^{90}Y). With ^{91}Y , forty of sixty-one cases had radiation pneumonitis and five had bronchioalveolar carcinoma. Insoluble ^{90}Sr showed thirty-four cases of radiation pneumonitis, sixteen pulmonary hemangiosarcomas, and eleven hemangiosarcomas of the heart out of seventy-four cases.

Even though the whole story is not yet told, these experiments to date indicate the very marked differences that can occur depending upon chemical form, not a new finding but one strongly reinforced by this work. *The experiments also isolated the contrasting effects of different elements, even isotopes of the same element.* That this latter occurs despite a relatively standardized system in which the aerosol parameters are essentially the same in each experiment bespeaks the importance of dosage pattern and other factors, such as energy, which are characteristic of the radioisotope in question. *These results alone are an argument for doing these long and expensive experiments.*

The experiments with inhaled ^{144}Ce in a relatively insoluble form in immature and aged dogs (see table 9.11) showed interesting similarities and contrasts to the young adults. With the immature dogs (ninety days of age at exposure), congestive heart failure was present in three of four dogs that died shortly after exposure (Boecker et al. 1979b). Also, pulmonary angiosarcomas occurred earlier and at lower radiation doses than in the animals exposed as young adults. No bronchioalveolar carcinomas had occurred at the time of reporting, but some were expected.

Other differences were seen with the aged dogs (Hahn et al. 1979c). Retention in the lungs was similar to that in young adults, but uptake by liver and skeleton was lower, especially in the latter. No hemangiosarcomas have developed to date in these animals, perhaps because the high dose needed to bring them about killed the older dogs with radiation pneumonitis. On the other hand, four pulmonary carcinomas have appeared, one of them causing the animal's death.

These differences, while not large, indicate, especially when combined with the experiments in rodents, that age at exposure can also play a role in the final results, at least with insoluble cerium. Since this work is less far along than the exposures of young adults, some modifications of the results may turn up in the future.

Cesium-137 has major health physics problems for handling as an aerosol. Because of its rather uniform distribution in the body, regardless of mode of entry, noted in earlier work, the Lovelace workers decided to administer it by intravenous injection. The results are reported in successive annual reports. They are not indicative yet of anything very special, viz., eleven cases of hematologic dyscrasia out of twenty-five exposed dogs that have died, and one squamous cell carcinoma of the maxillary sinus. The cumulative radiation doses to the whole body were from 690 to 2,200 rad in the twenty-five cases.

(a) There had already been work on cerium at Hanford.

b. Multiple Exposures

In general, there seems to have been considerable reluctance in the inhalation toxicology fraternity to enter upon long-term multiple exposure experiments with large animals. This is not surprising. Each single exposure is a fairly complex process. With hundreds of animals on line, simply keeping the single exposures up-to-date required large facilities and staff. Also, particularly in the earlier years, only limited amounts of the isotope of requisite purity were available. Handling large amounts at one time not only involved radiation hazards but was frequently not possible. It was quite different at Rochester, the home of the multiple-exposure experiment, where natural uranium was used for daily exposures five days per week. Supplies were ample and radiation hazards minimal.

Nevertheless, it was recognized that some occupational and many environmental exposures were either nearly continuous or in a series of single exposures. We have already seen that at Hanford Battelle undertook multiple inhalation exposures to transuranic elements. The Lovelace group introduced weekly exposures to ^{137}Cs -labeled FAP, ^{144}Ce FAP, $^{239}\text{PuO}_2$ in dogs, and $^{144}\text{CeO}_2$ in rats in the 1970s. (a)

The ^{137}Cs work (Boecker, Thomas, and McClellan 1975) involved twelve dogs each in groups receiving ten, twenty, or forty weekly exposures. The aerosol was insoluble and polydisperse, 1.5 to 2.0 μm , $\sigma_g = 1.5$ to 1.7. Average deposition percentages remained constant up to thirty exposures but fell off in the last ten exposures. As might be expected, a somewhat higher fraction of the body burden was found in the lung of the multiply exposed dogs. Autoradiographs showed that the ^{137}Cs remained associated with carrier particles for long periods after both single and multiple exposures. The most significant single difference in distribution and excretion was considerably longer retention after repeated exposures. Long-term whole-body retention ranged from twelve hundred to eighteen hundred days effective half-life compared to about four hundred days after single exposures. The result is a significant increase in cumulative radiation dose. No biological effect, including change in clearance rates from the lungs, was noted in this work since the observation period was not yet long.

A much longer-term multiple-exposure inhalation experiment was initiated in November 1973 using ^{144}Ce FAP. Exposures occurred once every eight weeks for two years. The retention was such that a fairly constant exposure to lung occurred. Although many of the animals are still alive, the results suggest that appearance of pulmonary tumors is delayed on the repeated exposure regime (Boecker et al. 1979a). For example, fifteen pulmonary tumors were seen in singly exposed dogs during the first twenty-two hundred days, while no pulmonary tumors appeared in the repeatedly exposed dogs. However, hemangiosarcomas and bronchioalveolar carcinomas began to appear later on. This reflects again the importance of dose kinetics in the temporal manifestations of effect.

Work with mice (Hahn, Lundgren, and McClellan 1980) showed a sparing of the life-shortening effect of $^{144}\text{CeO}_2$ in multiple exposures. *The protraction of dose had no effect on the total number of lung tumors seen or their time of development, i.e., total dose, not dose rate, seemed to be the important parameter.* This conflicts with our general knowledge of recovery and repair from exposure to low linear-energy-transfer (LET) radiation. However, it is consistent with some other work using beta-emitting radioisotopes. It may represent

(a) We will discuss the plutonium work in the following section.

a particular facet in a rather complex relationship between total dose and dose rate in radiation carcinogenesis as well as the fact that with internal emitters the dose never stops, as it does in experiments with external sources. It just varies in intensity. *The contrast between effects on life span and on carcinogenesis is consistent with other work on life-span shortening* (see chapter 4).

A repeated exposure study in rats was begun in 1976–1977, but the late results have not been seen.

4. The Alpha Emitters Come to Lovelace

With the enormous amount of work on plutonium, transplutoniums, polonium, radon and its daughter products, and radium already seen in several earlier chapters, it is hard to believe that still more could be needed. Yet it was, particularly around some of the problems of pulmonary radiotoxicology. The decision to emphasize light-water reactors and the uranium-plutonium fuel cycle (not an unmitigated blessing in this writer's view) and the consequent potential rise in amounts of plutonium and other transuranics needing storage, reprocessing and/or disposal brought ever more concern about the toxic effects of plutonium. The "hot particle" problem added much fuel to these concerns. We will discuss the problem itself in section V A below. Suffice it to say here that it was the hot particle problem that brought a new, fairly large research program on alpha emitters to Lovelace.

a. Monodisperse Aerosols

Kotrappa and Moss (1971) introduced a clever twist in the aerosol field. They used one of the devices developed for separating particles by size for characterization of aerosols into a method for preparing monodisperse aerosols. The device was Stöber's aerosol spectrometer, which is an aerosol centrifuge based on a spinning spiral. Large instead of small samples of a thermally degraded aerosol of FAP were collected on the metal strips on which the particles were deposited. Tyndall spectra plus electron microscopy and a Zeiss particle size analyzer showed good particle separation. The brass strip could be cut into sections depending upon the size range desired. After removal, washings, and transfers, the resulting solution could be made airborne in a Lovelace nebulizer. Count median diameters between 0.32 and 1.78 μm with geometric standard deviations no larger than 1.17 and usually lower were characteristic of the resulting aerosols.^(a) The best they could do was a geometric deviation of 1.03, and most had a somewhat larger range; however, it is common to consider aerosols with σ_g in the 1.1 range as monodisperse.

Kotrappa and Moss (1971) tried out the technique in animals with oxides of ^{238}Pu , ^{239}Pu , ^{241}Am , and ^{244}Cm . They measured respiratory deposition in a beagle dog and concluded that the technique could easily produce lung burdens well above the equivalent of a maximum permissible burden in man. They had thus solved one of the recurrent problems with monodisperse aerosols—insufficient quantities.

(a) This was only one of three methods used for preparing monodisperse aerosols at Lovelace (McClellan 1972). It was used the most because of its rather remarkable lack of multiplet formation (multiplets = result of coalescence of single particles into larger ones containing multiples of the single particles) and the amount of material it could produce. Further background can be found in Raabe (1970).

Kotrappa, Wilkinson, and Boyd (1972) presented a modification of the above procedure at the Hanford symposium on transuranics. This used a Lovelace Aerosol Particle Separator instead of the Stöber device. This is still a centrifugal method with an expanding spiral channel. A diagram of the device is given by Kotrappa et al. The resulting particles are, or can be, nearly spherical. It had some difficulty producing enough material for any large program in dogs using relatively low-specific-activity isotopes, such as ^{239}Pu . The authors suggest its most useful application might be with higher-specific-activity transuranics. However, further developments made it possible to use ^{239}Pu .

b. Initial Transuranic Experiments

Although the second paper cited above indicates that the development of the technique was specifically for transuranic elements, this was not quite the beginning of the major effort at Lovelace with alpha emitters. It was in 1974 that Tamplin and Cochran, and Tamplin and Geesaman (see section V A) launched the hot particle controversy as applied to the lung. The Lovelace people had begun exposure of dogs to transuranics before this time as described by McClellan (1972). However, it was not yet a major undertaking.

McClellan (1972) gives the status of the work with beagles using ^{241}Am and ^{244}Cm and comparison of their results with those on plutonium in several forms in the Hanford work. The *raison d'être* at this time was the need for work on these two transuranics in a large animal to extend the ideas developed from work with rodents. They confirmed, in the dog, the much greater transportability from lung of inhaled $^{241}\text{AmO}_2$, $^{244}\text{CmCl}_3$, and $^{244}\text{CmO}_{1.73}$ with transport to skeleton and liver. There was also considerable additional work on particle-size effects and some theoretical lung retention curves from monodisperse plutonium aerosols. Five proposed life-span studies with monodisperse aerosols and work with Syrian hamsters were described at this time (1972).^(a)

c. The Major Plan

Following the lines outlined by McClellan, a fairly elaborate plan evolved, but now with special additional emphasis on the hot particle problem. The monodisperse aerosol gave an opportunity to produce, at least initially, widely different local dose rates while maintaining reasonably constant average dose rates.

The relationship of these for ^{239}Pu and ^{238}Pu is shown in figure 9.27A, and the plan of the experiment is given in figure 9.27B.

Two monodisperse particle sizes were usually chosen for the work: $1.5\ \mu\text{M}$ and $3.0\ \mu\text{M}$ aerodynamic diameter, but with some work at $0.75\ \mu\text{M}$ also. Seventy-two dogs took part in the experiment with ^{238}Pu and 316 dogs and 480 Fischer 344 rats in that with ^{239}Pu , plus side experiments with hamsters, and recently the addition of immature and aged beagles as in the fission product work.

The Lovelace work became part of a grand plan. The Hanford experiments were using primarily polydisperse aerosols. Assuming other factors were reasonably comparable, this would produce a "smeared" dose as against a more discrete dose from the monodisperse aerosol.^(b) A third approach was work at

(a) Important other contributors to the monodisperse aerosol project were Drs. Otto Raabe and George Newton.

(b) The Lovelace people compared mono- and polydisperse aerosols in the same experiment to eliminate possible differences between the laboratories or at least to see if there were any, but the interlaboratory collaboration added a further dimension.

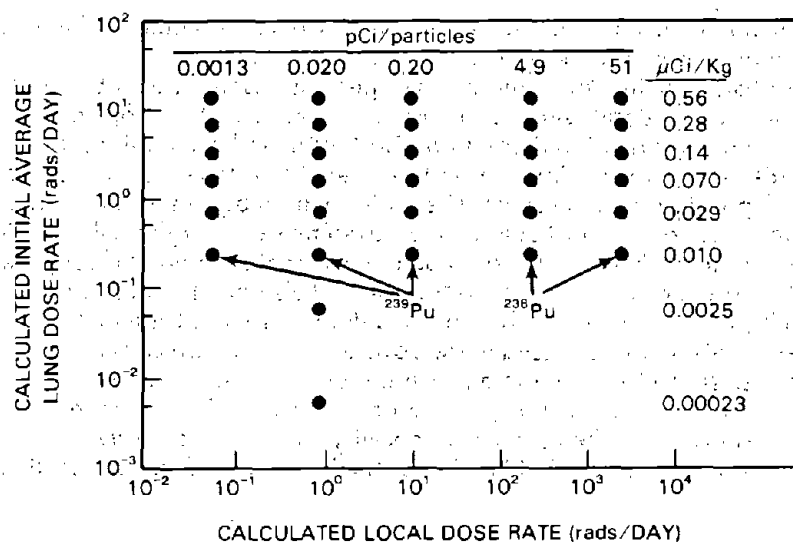


FIGURE 9.27A. Calculated dose relationships for the five planned dog longevity studies involving monodisperse aerosols of $^{238}(90\%)\text{PuO}_2$ or $^{239}\text{PuO}_2$. Local dose rate was computed in a $180\text{-}\mu\text{m}$ sphere of lung tissue (density = 0.22 g/cm^3). The calculation of average dose rate was based on a 110-g lung. Self absorption of alpha energy by the particles was ignored. (Redrawn from Muggenburg et al. 1979.)

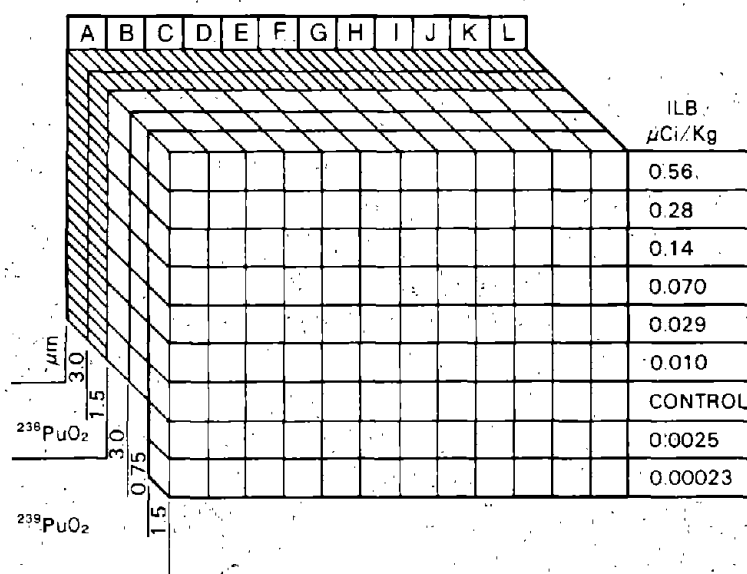


FIGURE 9.27B. Schematic representation of the experimental design of longevity studies involving dogs exposed to different monodisperse aerosols of $^{238}(90\%)\text{PuO}_2$. Each cube represents one dog entered into the experiment at 12 to 14 months of age. (Redrawn from Muggenburg et al. 1979.)

Los Alamos with microspheres of plutonium oxide/zirconium oxide injected intravenously, which we will review in later sections.

The pharmacokinetics of the monodisperse aerosols does not seem to have been studied in depth since emphasis was placed in this work on biological effects. What information there is on distribution and excretion of the Lovelace monodisperse aerosols does not indicate notable differences in items such as initial deposition, clearance, etc. There did seem to be almost equal amounts in liver and skeleton, somewhat in contrast to some work in other laboratories.

It seems likely that the processes of lung clearance would gradually make the polydisperse aerosols more monodisperse and also break up or polymerize the monodisperse products so that initial differences would gradually disappear. However, this is not addressed in the Lovelace work we are considering.

The results of these experiments were reported in the same way as the work with fission products, including a report on each animal in the appendix to each annual report. Since the results bear heavily, though not exclusively, on the hot particle problem, we will hold review of the biological effects for that discussion (section V A).

5. Miscellaneous

a. Facilities and Personnel

By the end of the decade of the seventies, the Inhalation Toxicology Research Institute had over two hundred personnel and had broadened the scope of its activities to nonnuclear problems. The facilities at South Sandia Base were able to house essentially all of the programs and were quite extensive. An aerial photograph of the Institute's layout at the end of the 1970s is shown in figure 9.28A. Steps in reaching this stage appear in figure 9.28B and 9.28C.



FIGURE 9.28A. The Lovelace facilities in September 1983. It was by then the Inhalation Toxicology Research Institute (ITRI) and had diversified into many areas of inhalation toxicology. (Photos courtesy of Drs. Roger McClellan and Bruce Boecker, ITRI.)

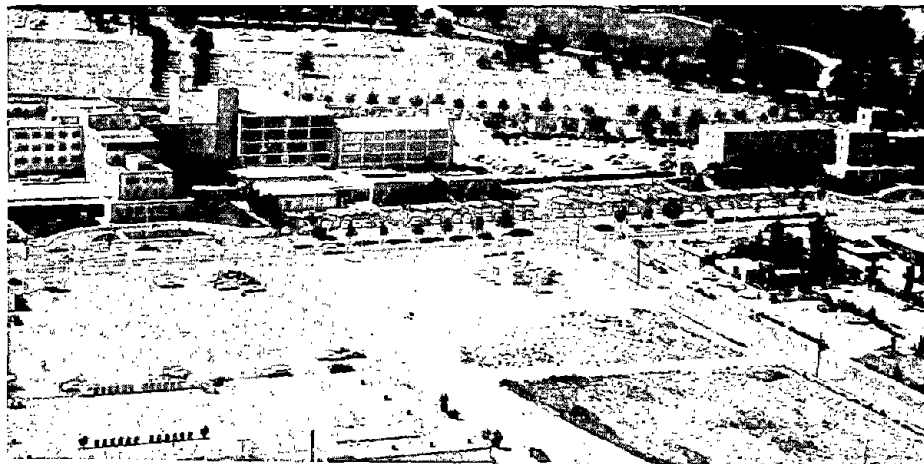


FIGURE 9.28B. The Lovelace Hospital and Clinic in which the inhalation toxicology work began. The problems of using radioactive materials, particularly aerosols, in this facility made the need for a more isolated facility urgent.



FIGURE 9.28C. The Lovelace project in August 1963, not too long after the inhalation exposure work had been moved out to the Sandia Base. Note the single holding pond at the upper right. This held weakly contaminated water and utilized the strong evaporative power of the desert sun to reduce greatly the volume of material needing disposal. The project was referred to then as the "MEC-1013 Project" or just the "1013" Project.

The personnel roster has stayed relatively constant in the senior ranks. Bob Thomas went to Los Alamos in the midseventies to help with their radiation toxicology program. Otto Raabe went to the University of California at Davis in the late seventies. Otherwise the names attached to the various progress reports represent well the senior staff at Lovelace in the nuclear energy field. The institute has expanded greatly into general inhalation toxicology around the problems of energy generation. The presence of strong aerosol and biomedical effects groups made the transition practical and productive.

b. Aerosol Research

In addition to the activities we have already seen, the aerosol group was busy doing field sampling and characterization at industrial sites, studying effects of thermal history of the aerosol on its properties (see Hanford description, also Thomas, Walker, and McClellan 1971 and Thomas et al. 1973), devising special exposure chambers, and exploring basic properties such as the charge characteristics of aerosols.

Particular note should be taken of work spearheaded by Otto Raabe and George Kanapilly. Noting the fact that deposited particles seemed to undergo dissolution as well as transport *in vivo*, they engaged for some years in studies of dissolution *in vitro*. Kanapilly et al. (1973) devised a system whereby solvents flow past particulate material collected on a membrane filter. A simulant of blood serum was devised, and dissolution of $^{144}\text{CeCl}_3$ particles, ^{95}Zr - ^{95}Nb , and ^{90}Sr FAP particles was measured. In general, the rates *in vitro* were comparable to those *in vivo* so long as the proper simulant was used. This technique was very useful in predicting behavior *in vivo* and was used in conjunction with lung modeling activities. A special lung-fluid simulant was devised by Raabe and used by him in a large number of experiments.

c. New Species

In addition to rat and dog experiments already cited, there was much work with Syrian hamsters. This included distribution and excretion of ^{244}Am and approaches to estimation of ^{241}Am body burdens *in vivo* (Thomas 1970). Biliary excretion of ^{144}Ce was also measured in the Syrian hamster. Carrier effects in ^{144}Ce aerosols were described along with the ubiquitous problem of chemical state.

d. Modeling

Partly as an outgrowth of the aerosol work and partly from the work on distribution and excretion, the Lovelace group has been active in devising metabolic models. Particularly they have presented models that expand a bit on the ICRP lung model, which we will discuss in chapter 16. Also, lung morphometry has been studied by preparation of elegant casts prepared by infiltration of plastic.

Lovelace conducted a six-year project for the National Institute of Environmental Health Sciences (NIEHS) under an interagency agreement between NIEHS and the DOE. This project involved *in-situ* casting techniques (over thirty-eight thousand records of airway characteristics) in four mammalian species; respiratory tract characteristics in the same species (human, dog, rat, and Syrian hamster); and animal inhalation studies. A detailed final report of this work was presented by Yeh (1980); it gives deposition models for the four species and details of the research. Among the findings are a partial explanation

for the higher deposition in the right apical lobe of mammals and why the alveolar surface area of dog and man are very similar despite the difference in body weight. The dog has three times as many alveoli as humans. Also, the respiratory structures of the Syrian hamster resemble the rat's, but the hamster has more anatomical dead space and thus lower deposition than the rat. The report concludes that the ICRP lung model overestimates deposition.

e. Physiological Aspects

In addition to the huge amount of biological information produced in the long-term experiments, many special studies were undertaken. Among these are functional studies, particularly of pulmonary and cardiovascular function; relationships among the various respiratory parameters as lung damage progressed; pathogenesis of the many lesions found in the exposed dogs; and biochemical studies (see, for example, papers by Pfleger et al. [1975] and Pickrell et al. [1975] on pulmonary lipid composition, physiology, pathology, and connective tissue alterations from chronic lung irradiation from ^{144}Ce FAP).

f. Cytogenetics

The development of chromosome aberrations in lymphocytes cultured from the blood of exposed animals has been watched carefully by Brooks and his colleagues. With ^{239}Pu , for example, using the rhesus monkey, LaBauve et al. (1980) found what seemed to be a threshold for this nonstochastic effect at about 1,000 rad. There was other work along these lines, which we will have to omit.

Some work was done in the field of immunosuppression brought about by radionuclides in lung and lymph nodes and some in vitro studies of the interactions of cells with the materials of interest along the general lines of Sanders's work at Hanford.

g. Thorium

Relatively recently, the Lovelace group has begun work on both distribution and excretion, and eventually effects, of elements of the thorium-uranium fuel cycle. For the moment, it will be largely characterization of the materials and their aerosols.

6. Commentary

There is no doubt that the Lovelace work accomplished its original purpose of studying inhaled fission product aerosols fully and completely. There is far too much detail in the reports to ferret out any way or ways in which the results brought complete surprises or markedly contradictory conclusions to what might have been anticipated from the earlier inhalation or from the intravenous work. This was not expected. Quantitative differences are numerous and, of course, everything is much more certain. The much larger doses of beta radiation needed for production of lung tumors, as compared to the alpha emitters, is comparable to that seen earlier for bone tumors. The unique position of plutonium has been maintained.

As the work continues to unfold, more and more final conclusions can be drawn.

C. University of Rochester

1. Generally Speaking

The University of Rochester's Department of Radiation Biology and Biophysics (originally Atomic Energy Project) qualifies fully as a center for postwar work in pulmonary radiotoxicology. However, the emphasis and programs differ significantly from the research at Hanford and Lovelace Inhalation Toxicology Research Institute, which we have just reviewed. Only one experiment, the long-term uranium experiment,^(a) would qualify as a "king-sized" experiment of the dimensions seen at the above laboratories, plus Utah and Davis. Some of the work with radon was long-term but involved primarily small animals.

The reasons for this difference were partly the lack of space to spread out referred to earlier, partly a disinclination to add any more production-line type experiments (many of the personnel had been through the war years and desired other approaches), and partly the perceived need for one center with more concentration on the basic physiological and pharmacological processes underlying the work at all laboratories. After all, the new centers, manned to a considerable extent by people from Rochester, were doing many of the needed long-term effects experiments under quite favorable conditions. The status of Rochester as a center for graduate and postdoctoral training in the field, already alluded to, had a large influence on these trends also.

Thus, although the Rochester postwar program began as essentially an extension of the MED work, it gradually changed in emphasis. The postwar work was not only very versatile, with efforts involving many aspects of air pollution research, but it was carried on by relatively small clusters of investigators with a neat balance of the needs of the marketplace and "pure" science.

2. Aerosol Science

We have already reviewed briefly the many contributions from the Rochester group in the earlier section of this chapter devoted to this subject. For the record, we might list some of the major developments, including instruments that came out of the Rochester effort, in either late MED or postwar days:^(b)

- a. Cascade impactor applications
- b. Application of Wright Dust Feed
- c. Selenium coating for electron microscopy
- d. Efficiency of electrostatic precipitators
- e. Lauterbach aerosol generator
- f. Four-channel continuously recording monitor for airborne alpha activity (Morken and Wilson 1960)
- g. Oscillating thermal precipitator (Lauterbach et al. 1952)
- h. Point-to-plane electrostatic precipitator (Morrow and Mercer 1964)
- i. Aerosol centrifuge (Stöber 1967)
- j. Special exposure chambers for radon (see chapter 3 and section on Alpha Laboratory)
- k. Special exposure chambers for radioactive aerosols (see Alpha Laboratory)

(a) A very large experiment at Rochester on the effects of x rays on fertility in the dog paralleled the uranium experiment, but it is not part of the inhalation toxicology story we are reviewing.

(b) Most were referenced in the aerosol section of this chapter. Other references are added in this section.

- l. Multiple chambers for chronic inhalation studies (see uranium experiment)
- m. Interactions of aerosols with radionuclides (Mercer 1973)
- n. Charge characteristics of aerosols (Mercer)
- o. Role of particle size in deposition and retention (see all sections).

This is to name just a few. Other developments in aerosol science are quite basic to the field but beyond our scope here.^(a)

3. The Long-Term Uranium Experiment

This eleven-year-long chronic exposure experiment was described in some detail in the chapter on uranium (chapter 2). It was most like the "king-sized" experiments elsewhere of all the postwar work at Rochester. The exposures were to UO_2 dust, five days per week for up to five years. Deposition, retention, excretion, and short- and long-term effects were observed in a variety of species for up to six additional years, as well as during the exposure period. Perhaps the most cogent finding for the field of pulmonary radiotoxicology was the fact that radiogenic effects could be produced with inhaled insoluble uranium if one worked hard enough and long enough. Indeed, pulmonary cancers were produced in some of the dogs, a first. Comparable depositions in the monkey did not produce cancer, but there was serious and widespread fibrosis of lung and pulmonary lymphatics.

4. Work with Radon

Rochester worked in the field of radon and its daughter products in two, quite separate activities. Both of these are described in detail in chapter 3.

The first is the enunciation by W. F. Bale of the importance of the radiation dose from preformed radon daughters *inhaled* along with radon in the atmosphere.^(b) This was followed by experimental verification, which was done by Bale and Shapiro (chapter 3).

The other radon enterprise in the postwar years was the experimental work of Donald Morken with pathology done by J. K. Scott. This began with a small chamber for exposing mice to an atmosphere with low daughter product activity. The results (chapter 3) indicated acute toxicity quite comparable to a similar calculated dose from x rays. This was a surprising result in view of the usually tenfold or more greater effectiveness of alpha particles compared to low-LET radiation. It has stood the test of time, however, and indicates a low relative biological effectiveness for radon in acute exposures in the mouse at least.^(c)

Later, a larger unit that could accommodate more and a larger variety of animals was developed. The experiments, which included mice, rats, and dogs, involved measurements of life-span shortening, hematological changes, and histopathology. Daughter products could be present and the exposures could be single or prolonged. The results (chapter 3) might be characterized as expected,

(a) It might be added that Dr. Lucien Dautrebande, frequently referred to as the father of medical aerosols and the designer of many aerosol generators, spent several summers with the Rochester group and prepared his book on microaerosols (Dautrebande 1962) during these visits.

(b) Bale and John Harley at the Health and Safety Laboratories in New York share the honor of developing this idea, but Bale's written version appeared first.

(c) Later work with daughter products present indicated the usual extra effectiveness of alpha particles, but not necessarily as high as a factor of ten.

except for the total lack of lung tumor development. Some metaplasia was seen, but the lesion characteristic of uranium miners seemed extraordinarily hard to reproduce in this type of experiment under the conditions used.

5. The Alpha Laboratory

In chapter 8, we remarked on the desires expressed at the time of the development of the Utah project to have Rochester mount an inhalation program. We saw also that Rochester was a prime candidate for the fission product inhalation project that went to Lovelace. The reasons these did not develop at Rochester have already been reviewed. Nevertheless, both AEC Headquarters staff and many of the Rochester investigators were convinced that there should be a facility onsite capable of handling aerosols of radioactive materials of higher specific activity than the uranium facility could accommodate. Because of the long-standing interest in alpha emitters at Rochester, it was decided to develop a laboratory designed basically for work with aerosols, which would not require much shielding against penetrating radiation. The decision was made in the early 1950s, and the facility was called "The Alpha Laboratory."

A new research section was organized within the Division of Pharmacology known as "The Radioactive Inhalation Section." It was this writer's privilege to be its section head and to participate in most of the planning^(a) and its operations from 1952 until 1959, when he was called to be associate director for education of the project and associate dean for graduate studies of the school, a change made advisable by the illness of Dr. Henry A. Blair, the project director. Senior staff of the Radioactive Inhalation Section at the time of organization were Dr. Paul E. Morrow, a pharmacologist-toxicologist who began there an illustrious career, which has brought him international recognition; Dr. Frank A. Smith, a biochemist who has probably done more work on the biochemistry, pharmacology, and toxicology of fluorine and the fluorides than anyone else in America; Dr. Donald A. Morken, a brilliant engineering physics graduate with intimate knowledge of electronics who became interested in the radon problem and has stuck with it ever since, in addition to training numerous students in the electronics behind radiation measurements; and Robert H. Wilson, an engineer of remarkable creativity who took part in essentially every major engineering development of the Rochester Project. The planning board consisted of most of the section heads: W. F. Neuman, a biochemist; A. Rothstein, a biophysicist-cellular physiologist; J. K. Scott, a pathologist; J. N. Stannard, a radiation biologist-pharmacologist; R. W. Wilson, the engineer; T. T. Mercer (and they do not come any better), for aerosol problems; and finally, a representative from Health Physics. All was under the general direction of the Pharmacology Division head, Dr. Harold C. Hodge. There were about twenty other staff members. When, in 1959, the University established a new and separate Department of Pharmacology and selected Dr. Hodge to be its chairman, and Stannard went to other duties, part-time at least, a reorganization took place toward smaller academic-type clusters. Nevertheless, the laboratory continued its service functions until the alpha-emitter work had run its course.

Since the Alpha Laboratory was unique in design and different in purpose from some of the other installations, we will review its characteristics briefly.

(a) Some of the planning was already under way.

The laboratory was a service facility meant to accommodate a variety of experiments of different investigator groups simultaneously or in tandem, as needed. While there were a few more or less standard "dry boxes," there were many specialized ones built to order for the purpose at hand. The basic design had the usual separation of "Clean," "Low-Risk," and "High-Risk" areas (called "White," "Green," and "Red"). Entry to the latter was through a change room. Entry to the former was through a monitoring station. There was a small space available in the red area for storage of "hot animals," self-contained dish and cage washing equipment; a separate but connected hood room in the green area with low- and high-activity areas; a counting facility in the "cold" area; and detachable laboratory benches along the walls of the green area. The "dry boxes" were connected to the "high-risk" (red) area, but could be operated from the "low-risk" (green) area.

The services of monitoring, some counting, autoradiography dark room, cleaning, and some animal maintenance were provided by the basic staff. Anything more special fell upon the group doing the experiment.

The facility was really a "poor man's hot laboratory." There was no stainless steel, only easily cleanable and easily replaceable plastic or painted surfaces. The basic construction was wood and plywood, which saved thousands of dollars, but introduced, of course, a fire hazard far above the usual stainless steel and concrete installation. To minimize the fire hazard, all heating was done by electricity or steam. All electrical circuits were fused at amperages only slightly above the load to be applied.

The light construction could be employed because only alpha emitters were to be used. (Even so, some of the aerosol generators required shielding, as did some of the primary stock sources.)

Protection depended entirely upon an ingenious and elaborate system of ventilation. Pressure gradients, as in all good hot laboratories, were always from low-risk to high-risk areas with the final exhaust going through Cambridge Absolute Filters to a stack with continuous monitoring. Because of the extreme importance of maintaining the pressure gradients, every important ingredient in the system was installed in duplicate. Pressure-sensitive sensors brought the duplicate unit into operation before the overall pressure gradient could change appreciably. Backing up all of this was a propane-operated motor generator set which would switch in automatically in case of power failure, even if only one phase of the three-phase electrical input should falter. In many years of operation, there was never an instance of failure of this ventilation system.

The details of the laboratory's design, considered unique in its ability to use inexpensive materials and to operate in a populous area on a university campus, are described in a series of University of Rochester Project Reports cited in the bibliography (R. H. Wilson et al. 1955; Smith, Della Rosa, and Casarett 1955; Morrow and Casarett 1955; Rothstein and Hayes 1957; Whipple et al. 1955; Morken and Morrow 1956).

Other developments were protective clothing of special design and self-contained breathing apparatus, the latter developed by Scott Aviation Corporation;^(a) also, a special neoprene glove for the dry boxes, which provided high tactile sensitivity without compromising integrity of structure (Wilson UR-265). A picture of the inner corridor (high-risk area) with workers in full protective

(a) Lancaster, New York.

clothing and a view of the low-risk (green) area are shown as figure 9.29A and 9.29B. A general floor diagram of the facility is shown as figure 9.30.(a).

FIGURE 9.29A. (Right) View of inner corridor of high-risk (red) area of Alpha Laboratory at the University of Rochester. Personnel are wearing full protective clothing and self-contained breathing equipment. The small tank on the latter could be supplemented by air under pressure from a quick disconnect plug in the ceiling. Note the communication cord is integrated loosely with the air hose.



FIGURE 9.29B. (Below) Part of the low-risk (green) area of the Alpha Laboratory at the University of Rochester showing dry boxes connected to the transfer corridor (high-risk area) and the moveable laboratory benches on the outside wall (right).

Photos courtesy of Photographic Department, University of Rochester Medical School.



(a) These pictures and diagrams are presented primarily because we have not viewed the facilities and needed personnel protection of a radioactive inhalation laboratory before. All of the installations have the same basic problems and similar ways to meet them, usually at higher cost because of the need for stainless steel and the like.

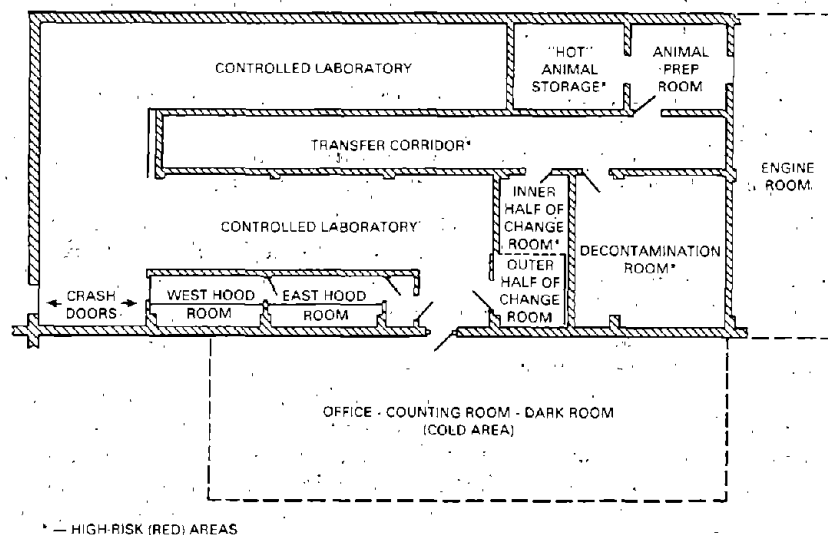


FIGURE 9.30. Floor plan of Alpha Laboratory. The controlled laboratory area is a low-risk but not a "cold" area. The high-risk (red) areas are marked with an asterisk. (Redrawn from R. H. Wilson et al. 1955.)

The specialized dry boxes varied from time to time. Typical are the original radon exposure units for small animals (see chapter 3); a sophisticated system for separating inhaled from expired air columns in the dog and measurement of both radioactivity and respiratory parameters remotely (Morken and Morrow 1956); a versatile unit for exposing animals to radioactive dust (Rothstein and Hayes 1957); nose-only exposure unit for polonium (Casarett 1964a); and others. We will review results of their use in subsequent sections.

There were, in addition, special design metabolism cages for keeping dogs in the high-risk area for short periods immediately after exposure (Morrow et al. 1967), special tongs for handling "hot" animals, etc.

The facility was used primarily for work with polonium, plutonium, and the radon experiment, which was next door but which shared some components. Later on, beta emitters such as ^{59}Fe , ^{192}Ir , and others were added, but not all such work was done in the alpha facility. The acquisition of two Air Force trailers left over from field work that we will see in chapter 14 expanded the facilities. One trailer was fitted out with well-counters and another was conveniently adapted to animal storage.

6. Inhalation of Polonium-210

In chapter 4, we reviewed the bulk of toxicological research on ^{210}Po . This included the fairly recent idea that the ^{210}Po in tobacco smoke might be a contributory, even a primary, factor in producing lung cancer in cigarette smokers. We did not consider in chapter 4 the MED or postwar work at Rochester on inhalation of ^{210}Po .

This work was conceived and done primarily to determine of the behavior and effects of this radionuclide after inhalation:

- a. for comparison with plutonium,
- b. because most of the significant dose from radon daughter products comes from isotopes of polonium,
- c. because polonium was still a potential industrial and environmental pollutant (in static eliminators, nuclear energy operations, etc.).

It was done well before the tobacco smoke possibility had been enunciated. The levels used were considerably higher than those found in tobacco smoke.

The Rochester work was led off by intratracheal injection of a freshly neutralized polonium solution in rats. This was first described in a project report by Thomas and Stannard (1956) and in detail in the *Polonium Supplement*^(a) (Thomas and Stannard 1964). This was paralleled by a comparison of ^{210}Po colloid with ^{210}Po -tagged silver particles given intratracheally to rabbits by Morrow and Della Rosa (1956) and a published paper (Morrow and Della Rosa 1964).

The experiment with rats was in three parts, short- and longer-term distribution after a single dose, and distribution and excretion after multiple intratracheal injections. The shorter-term distribution study went to sixty-two days, the longer-term distribution study to over four hundred days. Of considerable interest is the rapid loss from lung, the tendency toward a long period of constancy in the blood content, and widely different loss rates from different tissues. Kidney had the longest retention half-time, with liver, spleen, and gastrointestinal tract about one-third as long. These were all longer than after oral or intravenous intake.

On the multiple-dose regimen (one dose each two weeks for a total of five exposures), distribution and excretion were not the same as after a single instillation. The differences are indicated in figure 9.31A and B.

The work with the rabbit extended to thirty days. It demonstrated again rapid loss from lung and considerable accumulation in kidney. The most striking difference between rat and rabbit was in the urinary excretion rate. Whereas only about 1% of the dose appeared in urine after eight days, and only 2% after seventy days in the rat, the rabbit excreted 18% in eight days and 30% in the urine in thirty days. This species difference has been seen also after intravenous administration (chapter 4) and represents a fundamental difference in the handling of polonium. Tissue distribution patterns were similar in the two species.

Two metabolism experiments after inhalation of aerosols were done in the Alpha Laboratory following the intratracheal work. First reported was work using the large chamber described by Rothstein and Hayes diagrammed in figure 9.32 in which many animals were exposed "whole body," i.e., in a complete enclosure (Berke and DiPasqua 1957, 1960, 1964).

The second inhalation experiment was a "nose-only" exposure in rats by L. J. Casarett (1964a), which harked back in part to work done in his Ph.D. thesis. The idea of contrasting exposure modes was to determine what role the licking of fur and contamination of the head might have on total body burden. (This seems to be one of the few back-to-back experiments where this common dilemma of aerosol exposures was attacked directly.) The aerosol used by Casarett was quite small ($0.34\ \mu\text{MMD}$, $\sigma_g = 2.24$). Mean deposition was apparently higher in the nose-only experiment than in the chamber experiment and more

(a) Supplement 5 to *Radiation Research*, see chapter 4.

FIGURE 9.31A. (Right) Excretion of polonium after the last of five biweekly intratracheal injections (the points), compared with that after a single intratracheal injection (the lines). Symbols represent individual animals receiving multiple doses. (Redrawn from Thomas and Stannard 1964. Reprinted with permission of Academic Press, Inc., Orlando, Florida, copyright 1964.)

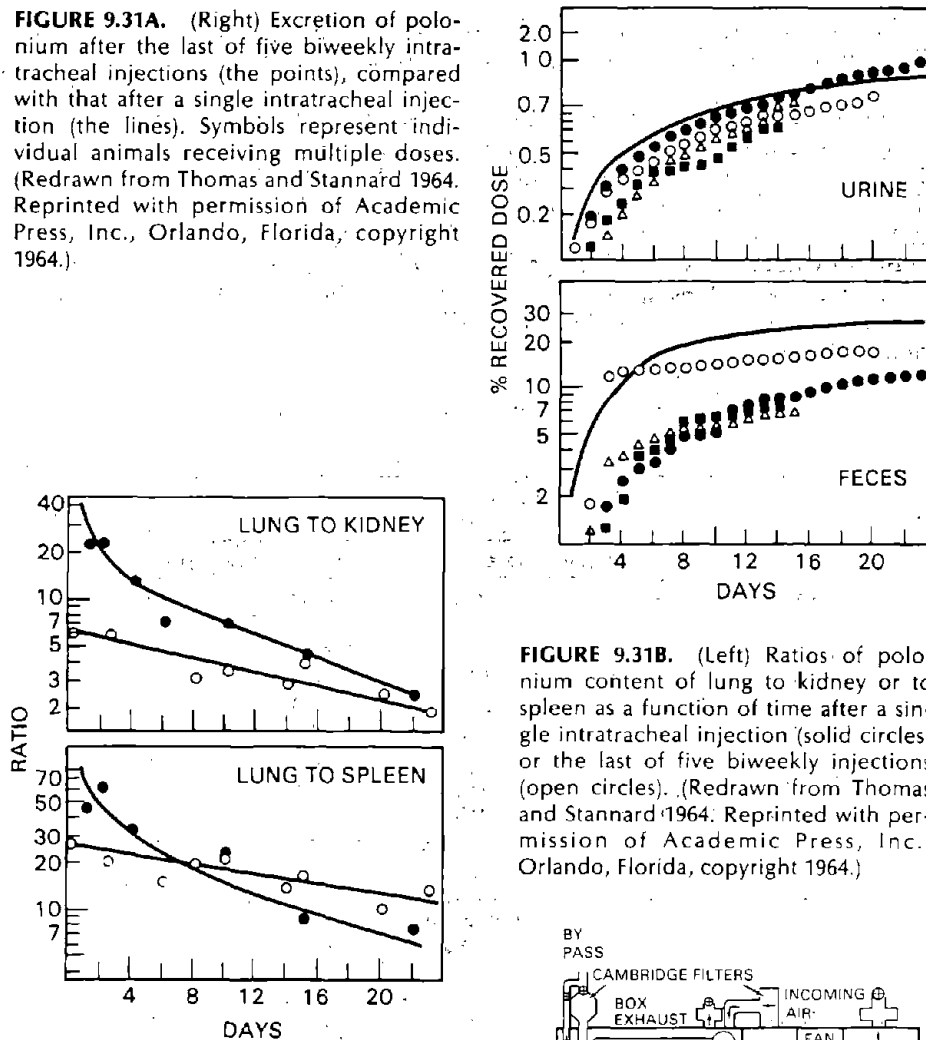
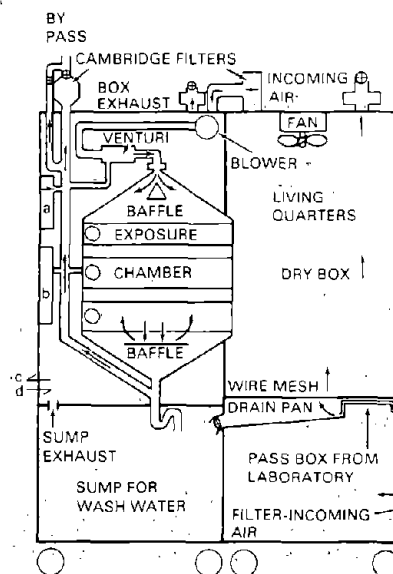


FIGURE 9.31B. (Left) Ratios of polonium content of lung to kidney or to spleen as a function of time after a single intratracheal injection (solid circles) or the last of five biweekly injections (open circles). (Redrawn from Thomas and Stannard 1964. Reprinted with permission of Academic Press, Inc., Orlando, Florida, copyright 1964.)

FIGURE 9.32. (Right) Exposure chamber designed by Rothstein and Hayes (1957): a) aerosol generator; b) sampling equipment; c) vacuum line (sampling); d) compressed air inlet. (Redrawn from Rothstein and Hayes 1957.)



like figures for the same sodium chloride vector in dog and man. The tissue distribution of the deposited material was almost exactly the same with the two types of exposure.

Both inhalation experiments showed tissue distributions that were qualitatively different from those observed after intratracheal injection. Some of the difference may be due to the fluid introduced into the lungs by the intratracheal injection, which made their weight as much as 100% above that of animals that had inhaled the material. However, the differences were not limited to the respiratory tract. These confirm again the validity of doubts held concerning the use of intratracheal instillation as a surrogate for inhalation, at least for metabolism experiments. An example of the differences between routes is shown in table 9.15A and B.

TABLE 9.15. Distribution of ^{210}Po to Tissues

A.				
Intratracheal Injection Versus Inhalation-30 Days After Administration				
Tissue	Percent Dose		Percent Body Burden	
	Int.(a)	Inh.	Int.(a)	Inh.
Lung	11.1	5.9	35.8	42.7
Kidney	5.8	1.5	18.1	13.0
Liver	3.2	3.5	9.9	5.3
Spleen	1.2	0.35	3.9	3.5
Carcass	5.5	2.0	15.1	16.3
Blood	6.2	2.0	19.2	21.1

(a) Intratracheal study of Thomas and Stannard (1964).

B.				
Comparative Values 30 Days After Administration by Various Routes				
Tissue	Percent Body Burden/Gram Wet Tissue			
	Oral	Iv.	Inh.	Int.
Lung	0.9	0.9	46.4	17.6
Kidney	2.8	4.9	7.9	10.0
Liver	0.9	0.7	0.7	1.1
Spleen	4.3	8.8	5.8	6.4
Whole blood	17.2	—	1.1	1.3
Carcass	0.2	0.2	0.1	0.08
Pulmonary lymph nodes	—	—	6.6	21.2

Source: Modified slightly from Casarett 1964a. Reprinted with permission of Academic Press, Inc., Orlando, Florida, copyright 1964.

Meanwhile, the team of Berke and DiPasqua was conducting multiple inhalation exposures in the rat (1960). This was to check the ideas already developed from intravenous injection work (chapter 4) and intratracheal instillation (Thomas and Stannard 1956, 1964), which indicated different tissue distributions

and different biological elimination constants when materials were accumulated in several exposures. Fifty rats were used with ten consecutive daily exposures of five hours each. The postexposure interval was fifty-four days.

The results as given are tied to their bearing on maximum permissible air concentrations and calculations of maximum permissible exposures and do not present an overt comparison of the metabolism on the two regimens. The authors point out that the lung burden rises linearly with time, with the equilibrium time calculated as 185 days. This is, of course, much longer than after a single exposure. While the data are useful for predicting accumulation from multiple doses, the period of observation is probably too short to allow the appearance of any real differences in metabolism, even if the authors had searched for them.

Detailed and exhaustive autoradiography was done on tissues from the rabbits receiving ^{210}Po intratracheally (Casarett and Morrow 1964) and the rats receiving it by inhalation (Casarett 1964b). The findings are comparable to those of Sanders at Hanford that we discussed earlier insofar as the role of macrophages is concerned. This work preceded that of Sanders. In fact, it was Casarett who, using several routes of administration, first described in detail the phenomena of dissolution of the large aggregates ("stars") of polonium as a function of time in the tissues (Casarett 1956, 1964b; also his M.S. and Ph.D. theses). This followed in more elegant fashion a lead from a twenty-four-hour experiment described by Gallimore, Boyd, and Stannard (1954).

The autoradiographic work goes far beyond what we can report here. It made clear that material entering by the lung was removed largely by phagocytosis and that solubilization of the colloids by macrophages and/or lymphatic elements played an important role. Despite being a nominally "soluble" compound, there was little evidence of direct passage of polonium from lung to the vascular system because of its colloidal nature as a polonium hydroxide. The autoradiograms give ample evidence of adherence of the material to bronchiolar and other surfaces and the marked irregularity of the deposition and subsequent movements. They emphasize how crude any early-time lung dosimetry calculations must perforce be. Fortunately, the progressive disorganization of the sunbursts during transport and clearance, an outstanding contribution of this work, can be interpreted to mean that eventually a more regular, less punctate pattern develops so that lung dosimetry for later times may be more realistic than for the early periods after deposition.

As the facilities of the Alpha Laboratory came into fuller use, it was possible to expose dogs to polonium aerosols on a sodium chloride vector. For these experiments, measurements could be made of the inspired and expired concentrations, of the respiratory characteristics of each animal, and many correlations could be made. This utilized the apparatus, locally known as the "retention rig," developed by Morken and Morrow (1956) and described also by Morrow and Casarett (1955). This depended in turn on a wireless transducer pneumotachograph described by Morrow and Vosteen (1953). A schematic diagram of this apparatus is shown as figure 9.33.

The results in terms of distribution and excretion were described first in a project report (Smith et al. 1960) and a year later in the open literature (Smith et al. 1961). The exposures were single and brief and involved six dogs. Deposition averaged about 64%, in excellent agreement with deposition in man of the same aerosol containing the vector only (Morrow et al. 1958), but considerably higher than in the rat. Clearance showed an initial rapid and later slower phase as in

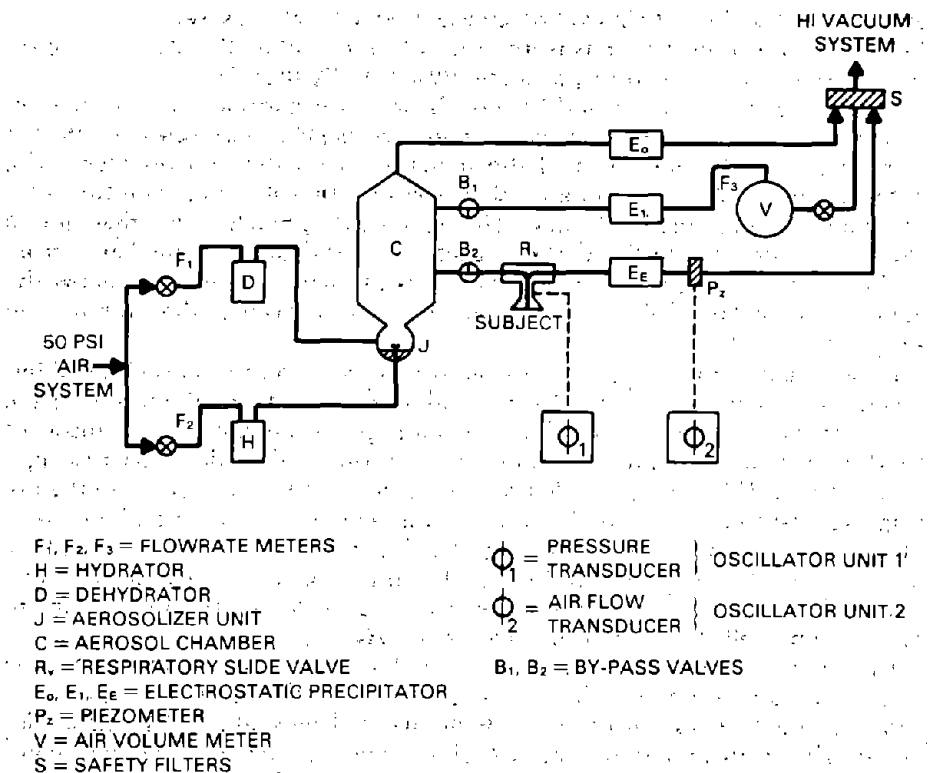


FIGURE 9.33. Schematic of retention apparatus developed at Rochester. (Redrawn from Morrow and Casarett 1955.)

the rat. The principal route of excretion was via the gastrointestinal tract. Exponential kinetics governed most of the loss patterns. While the tissue distribution patterns seem similar to those seen in the rat, the reliability of these data is much greater since the amount deposited is known by direct measurement for each dog. An interesting finding was the amount in the pelt, as much as 50% of the dose by 149 days—mostly in the hair follicles. (This could not have been from deposition on the fur, because the exposure was nose-only in the retention apparatus.) Clearance from the whole body seemed to be governed primarily by the rate of lung clearance.

Examination of long-term effects was possible in only a few experiments with rats. No long-term effects studies of inhaled polonium were done with dogs.

The first demonstration of lung cancer induced by ^{210}Po was contained in a quarterly report of the Atomic Energy Project (Scott and Thomas 1957). Two of fifteen rats developed squamous carcinoma 5 and 15 months after intratracheal injection. An extension (unpublished but quoted in the literature) showed production of six of these lesions in a group of forty-seven rats. The times were from 66 to 126 weeks after exposure.

Ten years later a true inhalation effects study was reported. The exposure chamber was the "whole-body" type described earlier. There were three exposure levels with fifty rats per level, and the postexposure period ran to 280 days.

The published report was produced by Yuile^(a), Berke, and Hull (1967). An easy summary of the results is contained in the abstract of their paper, which is reproduced below:

Inhalation by three groups of rats of NaCl aerosols with small amounts of Po^{210} added produced initial lung burdens of 0.15, 0.05, and 0.02 μCi . After 280 days, resulting accumulated lung doses were 538, 202, and 71 rads, respectively. Life span of the highest dose group was shortened, with 87% of the animals dying within one year after exposure, compared to 35% for controls and the other two experimental groups. Increased incidence and severity of acute pneumonia was the chief cause of the high mortality. Radiation changes in the lung were seen only in animals exposed to the highest level of radioactivity. No primary lung tumors developed in control rats, but 41 were found in 288 exposed rats dying spontaneously during the 96-week experiment. Squamous cell carcinoma was the commonest tumor type, accounting for 55% of the total number found. Over 70% of the squamous cell tumors occurred in rats exposed to the highest dose of Po^{210} , and many were early lesions associated with radiation injury. Pulmonary adenomas were seen only in rats exposed to low and medium doses. The highest dose appeared to be effective in preventing mediastinal lymphomas. (Yuile, Berke, and Hull 1967).

Not obvious from this abstract is the large number of deaths from chronic and acute pneumonia, a chronic problem in this and all other ordinary rat colonies. A picture of the spread in causes of death and the distribution of tumors by dosage level is shown in table 9.16A and B.

TABLE 9.16A. Summary of Pathological Findings After Polonium-210 Inhalation Excluding Neoplasms

Po^{210} Exposure Level	Total Number of Rats Exposed ^(a)	Age Range at End of Experiment (weeks)	Number of Spontaneous Deaths	Significant Nonneoplastic Pulmonary Lesions (% of rats dying spontaneously)			
				Chronic Pneumonia	Acute Pneumonia	Radiation Changes	Epithelial Metaplasia
Control 0 μCi	147	87-100	88	23	25	0	4
High 0.15 μCi	119	106	119	21	65	32	17
Medium 0.05 μCi	129	95-100	98	22	50	0	9
Low 0.02 μCi	132	89-91	71	25	45	0	4

(a) Corrected for those sacrificed.

TABLE 9.16B. Tumor Incidence and Type

Po^{210} Exposure Level	Primary Lung Tumors Total Number	Rats Bearing Tumors		Tumor Types—Total Number			
		Total Number	% of Total Exposed	Squamous Carcinoma	Carcinoma, Other	Mesenchymal	Adenoma
Control 0 μCi	0	0	0	—	—	—	—
High 0.15 μCi	22	15	13	17	3	2	0
Medium 0.05 μCi	15	13	10	5	3	2	5
Low 0.02 μCi	4	4	3	1 (trachea)	0	0	3

Source: Reset from Yuile, Berke, and Hull 1967. Reprinted with permission of Academic Press, Inc., Orlando, Florida, copyright 1967.

(a) Dr. Charles Yuile had taken over the histopathology work done by Dr. J. K. Scott after he went to the Lovelace Foundation.

Quite obviously, these doses of polonium produce significant changes in lung, but unequivocal radiation changes and frank tumors are not overwhelming. Superficially this looks as though changes from polonium are less pronounced than those from plutonium (see studies elsewhere already reviewed). However, the period of observation was relatively short and the radiation doses relatively modest compared to the enormous doses we have become accustomed to in the dog experiments done with plutonium. Indeed, it appears that polonium is a moderately potent pulmonary carcinogen, either primary or secondary.

7. Inhalation of Plutonium

Inhalation work with $^{239}\text{PuO}_2$ began at Rochester in 1958. The facilities of the Alpha Laboratory were used for exposing dogs via the retention apparatus with the intent of measuring deposition more precisely and performing an intensive autoradiographic investigation of the tissues of the respiratory tract. The first report of results (except for in-house progress reports) came out at the Oxford symposium on Inhaled Particles and Vapours, March-April 1960 (Morrow and Casarett 1961). There were twenty-one experimental measurements in seventeen dogs using in-vivo counting for some of the points. The exposures were single. The aerosol characteristics varied from 1.7 $\mu\text{Ci/l}$, count median diameter 0.24 μ , σ_g 1.81 for the first seven exposures to 0.9 $\mu\text{Ci/l}$, count median diameter 0.70 μ , σ_g 1.77 for the balance of the exposures.

With the benefit of precise measurement of inhaled and exhaled air concentrations, deposition could be calculated with considerable confidence. With the small-sized aerosol, mass deposition was 56%, whereas it was 88% with the larger particle size aerosol. It seemed not to be related to the measured respiratory parameters within the range of this work. (It is, of course, impossible to train animals to hold their breath, take a deep breath, etc., which has made possible much of the information in humans on the role of respiratory parameters on deposition.)

A size analysis of the particles retained in the lung was performed, including the relative numbers of particles in various anatomical regions of the lower respiratory tract. The smallest particles were retained the longest. Excretion was largely in the feces, as expected.

The autoradiographic work showed very clearly that all known mechanisms of lung clearance were operable. Of special interest are autoradiograms of plutonium in the peribronchiolar lymphatics and an excellent illustration of the constantly frustrating difference in content of closely adjacent lymph nodes. (How can we ever decide what fraction of the lymphatic system is involved in chronic low-dose exposures and therefore what weight to assign to it for dosage calculation? Examples of these facts are shown in figure 9.34A and B.)

A more extensive inhalation study with plutonium (Morrow et al. 1967) involved twenty-two dogs. It was built upon the first one and includes some of the same animals. Plutonium-238 was used as was ^{239}Pu . Among other things, the problems of radiochemical analysis for plutonium were reexamined and new procedures adopted based on work of Toribara and colleagues (Toribara, Predmore, and Hargrave 1962; Toribara, Morken, and Predmore 1962). Emphasis was on clearance kinetics and mechanisms and on the early pathologic effects.

Clearance seemed to be biphasic and exponential to time with biological half-times of one and four hundred days. Bronchial lymph nodes and lung carried 95% of the body burden.

FIGURE 9.34A. (Right) Autoradiogram of lymphatic vessel and lymph nodes demonstrating the distribution of plutonium oxide dust particles in the dog—peribronchiolar lymphatics containing plutonium particles. (At least fifty-two particles are registered in this field.) (From Morrow and Casarett 1961. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1961.)

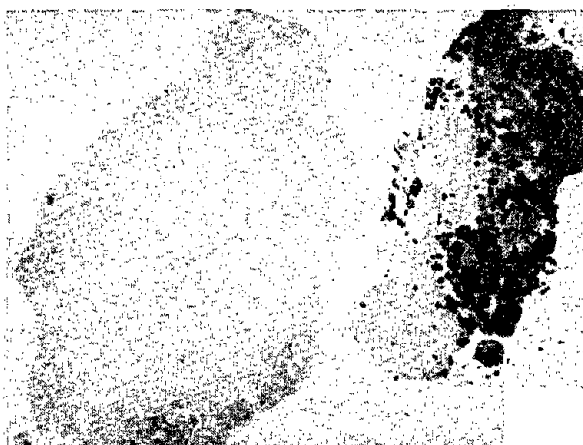
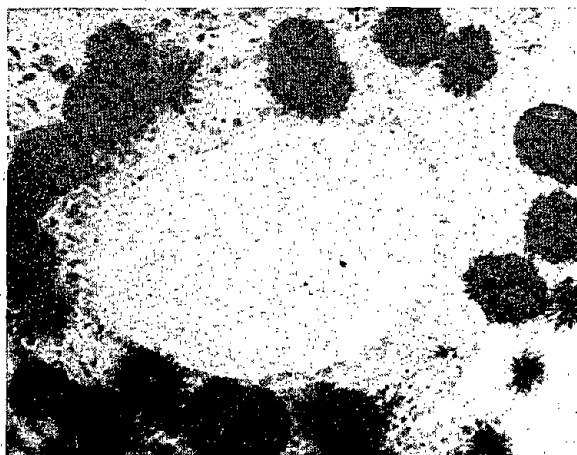


FIGURE 9.34B. (Left) Autoradiogram of lymphatic vessel and lymph nodes demonstrating the distribution of plutonium oxide dust particles in the dog—lymph nodes illustrating variable content of plutonium. (From Morrow and Casarett 1961. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1961.)

However, gonads appeared to receive significant radiation doses, raising again the question that came up in the early Hanford work as to the possibility of genetic changes. On the other hand, liver doses were quite low, in contrast to many other experiments we have seen.^(a) Similarly, relatively little plutonium was transported from lung to bone. These phenomena demonstrate the marked difference between inhalation and other routes of entry insofar as tissue distribution is concerned.

Kinetics of excretion were examined in depth and the presence of power-function-of-time kinetics reaffirmed. This has important bearing on the bioassay procedures of the past and present (chapter 7, 16). The authors engage in a detailed analysis of the excretion data and just how they do and do not fit the formulations of the day. Because of the relatively exact knowledge of deposition,

(a) It should be remembered that this work was well under way when the large efforts at Hanford and Lovelace came up to full speed, and it served as an important resource for these.

individual excretion curves could be drawn for each dog (Morrow et al. 1967, figure 10). Each one fitted power-function kinetics, but not with the same exponent.

Of considerable interest are the finding of progressive lymphopenia, beginning as early as two months postexposure, and focal pulmonary fibrosis. More complete information had to await further work, however.

The story was completed insofar as Rochester work was concerned with an experiment using both ^{238}Pu and ^{239}Pu . This extended out to 468 days after exposure (Yuile, Gibb, and Morrow 1970). There were nineteen dogs exposed to ^{239}Pu and six to ^{238}Pu . Doses ranged from 0.1 to 14.4 μCi initial lung burden of ^{239}Pu , and 11.4 to 181 μCi of ^{238}Pu . Since by this time the Hanford work was coming to fruition and being published extensively, there was much opportunity for comparison of results. As in other cases, the Rochester work emphasized mechanisms and, because the finding of early and constant leukopenia turned up in the Hanford dogs also, an extensive hematological study was included.

A grading system for the histopathology was devised for both lung and lymph node changes, and thus the degree of effect could be correlated with dose. Beginning at about 2,000 rad calculated dose, the radiation pathology in lungs rose steadily with dose up to about 15,000 rad (figure 9.35A). The lymph nodes showed no changes until radiation pathology was evident in the lungs. The development of damage from that point on correlated very poorly with calculated total dose to the lymph nodes. However, correlation with the alpha dose rate was as good as the correlation between total dose and lung damage. This unusual and most interesting finding is depicted in figure 9.35B.

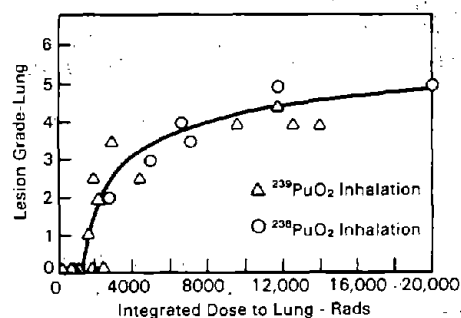
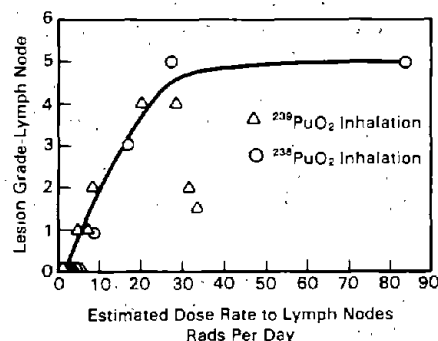


FIGURE 9.35A. (Left) Degree of radiation changes in lungs and lymph nodes graded on scale of 1-5, following $^{239}\text{PuO}_2$ and $^{238}\text{PuO}_2$ inhalation, related to accumulated lung dose in rads. (Redrawn from Yuile, Gibb, and Morrow 1970. Reprinted with permission of Academic Press, Inc., Orlando, Florida, copyright 1970.)

FIGURE 9.35B. (Right) Degree of radiation changes in tracheobronchial lymph nodes graded on scale of 1-5, related to mean dose rate to lymph nodes in rad per day after inhalation of $^{239}\text{PuO}_2$ and $^{238}\text{PuO}_2$. The two $^{239}\text{PuO}_2$ points which appear lower than the general trend are regarded as unreliable. (Redrawn from Yuile, Gibb, and Morrow 1970. Reprinted with permission of Academic Press, Inc., Orlando, Florida, copyright 1970.)



A correlation with dose rate was unusual with alpha emitters at this time. In general, a large portion of the biological damage from alpha particles was considered to be irreversible, and dose rate effects small compared to low-LET radiation.^(a) This is discussed by Yuile et al., but they could muster no ready explanation for this apparent exception to a maxim of radiobiology. The phenomenon has been described in the work from other laboratories (see chapter 1) using human data in effects of ^{224}Ra that indicated increased effect with protraction. It seems quite unlikely that it is a trick of the data for this particular experiment. Thus, for the present, we must accept it as it stands and hope an explanation can be found in future work.

The other key finding in the Rochester plutonium pathology work concerns the origin of the leukopenia. On the basis of the extensive autoradiographic studies of the deposition and localization of plutonium, the investigators conclude that the leukopenia cannot arise from radiation effects in hematopoietic tissues, the usual mechanism with external penetrating radiation. They suggest instead that the radiosensitive small circulating lymphocytes receive their radiation damage during transit of the lungs and adjacent lymphatics. Since nearly every small lymphocyte passes through the lungs and recirculates rapidly between blood and lymph via nodes and spleen (see discussion in cited references from the literature), there is ample opportunity for the alpha sources to irradiate them and thus initiate cell destruction.

Little is said in this work about metaplasia, lung-tumor development, and the like. Obviously, the experiment was not of sufficient duration to provide reliable incidence data for these processes. It was not intended to, for the work at Hanford and Lovelace was covering the longer-term area adequately. No need was seen to expend animals, money, and time at Rochester to go beyond the probing into the specific problems and mechanisms we have already seen.

8. Miscellaneous Experiments and Elements

Rochester was considered throughout the existence of the AEC as a prime resource for investigating new and unexpected toxicology problems. When a new substance or radionuclide appeared about to assume practical importance, the Rochester group was frequently asked to advise (as soon as possible, of course) on any potential toxicity problems that might arise should the substance go into routine use. Some of this extended into the inhalation toxicology effort. As a result, a rather miscellaneous group of elements and compounds were investigated on request. Fortunately, in nearly every case, information of importance to the basic fabric of pulmonary radiotoxicology was frequently a by-product of these "command performances." Most of these reports were in the form of communications to Washington and are not available for general use now, but several are cited below.

Some of the staff from the radioactive inhalation program became involved in work concerning field releases of both plutonium and fission products, as we will see in chapter 14. By-products of the problems encountered in this work stimulated some additional laboratory investigations. These appeared in the project reports. Some were published. Some rested as essentially "memos to the files." Finally, there was much work done only because the investigator had an

(a) There are now many reports of enhancement of effect by protraction of alpha dose. Their explanation may lie in factors other than cellular recovery phenomena.

idea he wanted to check on, and the work fitted easily into the program. Many of these bore on lung clearance processes. By using a convenient isotope, data could be obtained with relative ease.

In toto, these miscellaneous efforts produced useful and interesting information. The following are samples:

1. *Metabolism of Thorium-230 (Ionium) Administered by Intratracheal Injection to the Rat* (Thomas 1957)
2. *Retention and Fate of Iridium-192 in Rats Following Inhalation* (Casarett et al. 1960)
3. *The Metabolism of Indium after Administration of a Single Dose to the Rat by Intratracheal, Subcutaneous, Intramuscular and Oral Injection* (Smith, Thomas, and Scott 1960)
4. *The Distribution and Excretion of Thallium-204 in the Rat, with Suggested MPC's and a Bioassay Procedure* (Lie, Thomas, and Scott 1960)
5. *Alveolar Clearance in Dogs after Inhalation of an Iron-59 Oxide Aerosol* (Gibb and Morrow 1962)
6. *Deposition and Fate of Inhaled Iron-59 Oxide* (Casarett and Epstein 1966)
7. *The Metabolism of Inhaled Mercury Vapour in the Rat Studied by Isotope Techniques* (Hayes and Rothstein 1962)
8. *The Excretion of Volatile Mercury by Rats Injected with Mercuric Salts* (Clarkson and Rothstein 1964)
9. *The Clearance of Uranium Dioxide Dust from the Lungs Following Single and Multiple Inhalation Exposures* (Morrow, Gibb, and Leach 1966)
10. *Measurement of ^{212}Pb Loss Rate from Human Lungs* (Hursh and Mercer 1970)
11. *Inhalation Studies of Uranium Trioxide* (Morrow, Gibb, and Beiter 1972)
12. *Effect of SO_2 on Lung Clearance of TiO_2* (Ferin and Leach 1973)
13. *Experimental Inhalation of Metallic Silver* (Phalen and Morrow 1973)
14. *Intramuscular Retention of UO_3 and UO_2* (Beiter, Gibb, and Morrow 1975)
15. *Studies on Tantalum Dust in the Lungs* (Bianco et al. 1974)
16. *The Uptake and Retention of Insufflated Tantalum in Lymph Nodes* (Kilpper et al. 1976)

9. Mechanisms and Modeling

We have intimated throughout this section that the Rochester work was especially oriented toward the physiological and pharmacological mechanisms underlying all problems in inhalation toxicology, especially pulmonary radiotoxicology. The literature of the field is huge. Yet, we can look briefly at some of the high points.

Local, national, and international work was drawn upon to prepare a number of definitive reviews, which have been and continue to be extremely useful. Quantitation was emphasized wherever possible. With T. T. Mercer down the hall, few opportunities for formulation of relationships were lost. One of the most outstanding among these was the development of a new and much more sophisticated model for respiratory-tract deposition, clearance, and general characteristics to replace the simple model used in the 1950s and early 1960s (see chapter 16). Paul Morrow was asked to head a Task Group on Lung Dynamics of the International Commission on Radiological Protection working under its Committee 2. Tom Mercer joined him so that two of the five members came from Rochester.^(a) The resulting publication (Task Group on Lung

(a) The others were David V. Bates, Royal Victoria Hospital, Montreal; Birney R. Fish, Oak Ridge National Laboratory; and Theodore F. Hatch, University of Pittsburgh Graduate School of Public Health.

Dynamics 1966) was a quantum jump in quantitation and sophistication from the previous model. With a few modifications, it is now the official ICRP model and has been adopted for U.S. practices. It is a keystone in radiation protection planning. We will review it further in chapter 16. Suffice it to say here that the emphasis at Rochester on getting solid data and ideas on pulmonary kinetics—with collaboration from a Physiology Department with a strong respiration group—contributed strongly to its successful construction.^(a)

We will close this review of the mechanisms and modeling activities at Rochester with a listing of some of the cogent reviews and pertinent discussion papers. These are in addition to the reviews provided at the termination of the MED days in the Uranium Monograph and reviews cited earlier in this chapter. They are in more or less chronological order:

1. *Retention of Submicron Aerosols in the Human Respiratory Tract* (Stannard and Morrow 1956)
2. *An Evaluation of Inhalation Hazards in the Nuclear Energy Industry* (Stannard 1959)
3. *Some Physical and Physiological Factors Controlling the Fate of Inhaled Substances. I. Deposition* (Morrow 1960); *II Retention* (Casarett 1960)
4. *Alveolar Reactivity Following Inhalation of Particles* (Casarett and Milley 1964)
5. *Evaluation of Inhalation Hazards Based upon the Respirable Dust Concept and the Philosophy and Application of Selective Sampling* (Morrow 1964)
6. *On the Role of Particle Size in the Dissolution of Lung Burdens* (Mercer 1967)
7. *Dose to Respiratory Tract After Continuous Inhalation of Radioactive Aerosols* (Kotrappa 1968)
8. *Models for the Study of Particle Retention and Elimination in the Lung* (Morrow 1970)
9. *Lymphatic Drainage of the Lung in Dust Clearance* (Morrow 1972)
10. *Observations Concerning Alveolar Dust Clearance* (Ferin 1972)
11. *The Deposition Model of the Task Group on Lung Dynamics: A Comparison with Recent Experimental Data* (Mercer 1975)
12. *Clearance Kinetics of Inhaled Particles* (Morrow 1977)

All but the first item involve review and analysis of research as the field developed with small additions of new research. Perusal of these should give a comprehensive and penetrating review of the field of this chapter, particularly since they quote work from all of the major laboratories in the United States and abroad. Any further discussion is impossible here, but the interested reader wishing an overview of the physiology and pharmacology separate from the details of behavior of elements of special interest to internal emitter toxicology will profit greatly by tracking them down.

D. Other Laboratories Contributing to Pulmonary Radiotoxicology

1. Overview

Several laboratories that were (and are) centers for research in the general fields of inhalation toxicology and aerosol science mounted significant efforts in pulmonary radiotoxicology. However, these were not on the all-consuming scale of

(a) Obviously, the years of work of the entire industrial dust fraternity played their role. This was not exclusively a Rochester show, but the Rochester talent and atmosphere played a key role.

those we have been discussing. Usually the work with the inhalation of radioactive materials in these laboratories involved fewer people and resources, was directed toward special problems or collaboration with other groups on special aspects of a larger problem. We will look briefly at the general nature of their contributions in this section. It will be obvious that some of the work is almost identical in concept to that carried on at what we have chosen to call "Centers," but on a smaller scale. Some is largely supportive to other groups. Some is mainly applied and directed toward engineering and control operations more than laboratory research. Because of the already ponderous amount of information we have had to review in this chapter, some of the contributions of these other laboratories will have to be presented largely by comparison of concept and results to the research we have already reviewed. Others will be discussed primarily in connection with the special problems that brought them into the field.

2. Harvard University

The Harvard School of Public Health has always had strong programs in the inhalation field, especially around the problems of ventilation, toxic gases, and air cleaning. Indeed, the periodic Harvard Air Cleaning Conferences are now an institution. We have noted that Philip Drinker, Professor of Industrial Hygiene at Harvard is coauthor with Hatch of "Industrial Dust" (1954). Leslie Silverman developed a myriad of methods in industrial hygiene. However, Harvard did not become deeply involved in pulmonary radiotoxicology. There were some significant contributions, primarily from one man.

Professor John B. Little got interested in the tumorigenicity of ^{210}Po . This was when work on the hot particle problem was rife and the promise of the Syrian hamster as a better test object in the rodent family than the rat was fading (see section V A). Little, Grossman, and O'Toole (1970) administered relatively small doses of ^{210}Po intratracheally to the hamster. The resulting crop of lung tumors and related pathology dispelled any doubts that the hamster could develop pulmonary cancer. With a calculated dose of 4,500 rad to whole lung, bronchogenic carcinomas appeared in 91% of the hamsters. They also induced carcinomas with the chemical carcinogen, benzo[a]pyrene (BaP). Later, McGandy et al. (1974) in Little's group demonstrated that the alpha-particle radiation plus BaP produced over twice the prevalence of lung tumors expected from either agent alone. In a later work, Little, McGandy, and Kennedy (1978) found that this apparent synergistic action, which was most characteristic when the BaP followed four months after the ^{210}Po , could be induced almost as well by instillations of 0.9% NaCl solution. Thus, we are again reminded that nature gives up her secrets with great reluctance. A seemingly innocuous stimulus may potentiate carcinogenesis—not a new finding, but new in this context. Little, Grossman, and O'Toole (1973) compared the effectiveness of ^{210}Po diluted in saline or after incubation with hematite particles ($0.75\text{-}\mu\text{m}$ mean diameter) as a carrier. The doses were multiple given over from seven to fifteen weeks. The polonium remained attached to the hematite particles, as demonstrated by autoradiography (also see Kennedy, Worcester, and Little 1977) and delivered a nonuniform dose to the lung, while the polonium in saline gave a much more uniform dose. It appeared that the hematite-bearing particles, while not carcinogenic in themselves, produced tumors somewhat earlier than the polonium in saline. On the other hand, when the dose and its distribution in space were manipulated, a lower but more uniformly distributed dose delivered to a larger volume of lung

tissue was more carcinogenic. This presents a dilemma that we will review further in the discussion of hot particles (section V A).

During this time, the question of radioactivity in tobacco smoke was coming to a head. Little's work contributed also to this, as we shall see in section V B.

Meanwhile, at the Harvard Medical School, Shields Warren, the dean of radiation pathologists, was interested in reactions of the lung to implanted radiation sources. It was Dr. Warren who sounded the alarm in the prewar years concerning radiation pneumonitis resulting from the ever-increasing energies and doses being used in x-ray therapy (Warren and Gates 1940). Warren and his long-term colleague Dr. Olive Gates implanted wires impregnated with ^{60}Co in the lungs of young adult rodents (Warren and Gates 1968). They compared eight strains of mice, Syrian Golden hamsters, guinea pigs, rats, and rabbits. Of 363 animals treated, about one-third developed bronchiogenic or epidermoid carcinoma. The rat, guinea pig, and rabbit also developed bone tumors. The mean total doses ranged from 8,500 r to 1,900,000 r.^(a) The lowest dose associated with cancer was 14,700 r. The rat seemed to be the most sensitive species. The histogenesis of the lung carcinomas was described in detail by Gates and Warren (1961). This paper contains also a useful table summarizing work to date on lung cancer production in rats.

This was part of a widespread interest in pulmonary cancer from implanted sources, as we will see presently.

3. Health and Safety Laboratory—Environmental Measurements Laboratory, New York City

We saw the involvement of this AEC-ERDA-DOE laboratory in radon work in chapter 3 and some of its general contributions to postwar research with internal emitters in chapter 8. The Laboratory devoted much of its effort to the development of methods and instrumentation, which were useful in a variety of programs both basic and applied. Apropos of inhalation problems, HASL was involved early in evaluation of inhalation hazards from uranium, thorium, beryllium, and other dusts in AEC-contractor installations and some independent companies (thorium). It took these duties over from Rochester at the end of the MED era. HASL has been a major contributor to evaluation of aerosol sampling methods and the development and perfection of air filter systems. When the fallout problems hit AEC, HASL became a major center for collecting, measuring, and evaluating fallout at both local and worldwide levels. It played a key role in health aspects of nearly every weapons test in both the Pacific and Nevada. (Details will be reserved for chapter 12.) HASL had much to do with making and evaluating environmental surveys, including the SNAP program, contamination around contractor plants, and the like. These included concern for inhalation hazards wherever they seemed important. Many of these will appear when we enter the environmental section of this book. In addition, in the middle years, HASL sponsored a number of training courses and symposia, mostly in applied fields.

HASL was involved directly in only a few laboratory experiments in the radioactive inhalation field. One of these, which came quite early (1950), was a study

(a) The expression of these doses in roentgens indicates that the work was done before the time of the full transition to rad and rem for all but external low-LET radiations.

of the elimination of inhaled radon (HASL-32). Another was the uranium dust clearance experiment in man carried out by Harris in 1960 and discussed in chapter 2.

Names to be associated with the contributions of HASL to inhalation toxicology are, among others, Merrill Eisenbud, John Harley, William Harris, Morton Lippmann, E. P. Hardy, Roy Albert, and A. J. Breslin.

Among the more general contributions are papers by Eisenbud on inhaled particles (Eisenbud 1952; Eisenbud and Quigley 1956) and the pertinent chapters in Eisenbud's book, *Environmental Radioactivity* (Eisenbud 1973). The many contributions of the Harleys on radon were seen in chapter 3, and those on fallout and the environment will be seen in chapters 12 and 13. An important review of natural radioactive materials in air appears in the chapter on inhaled radioactivity in NCRP report 45, which was prepared by a committee chaired by Dr. Harley (NCRP 1975b). Another example is the work on size-selective samplers described by Lippmann and Harris (1962).

Interest is still strong at the laboratory, now the Environmental Measurements Laboratory, in dust problems of industry and the environment, but it continues to involve primarily measurement, evaluation, and protection measures.

4. The Los Alamos Scientific Laboratory (LASL)

In the previous chapter, we saw that Los Alamos made major contributions to internal emitter toxicology in the postwar era. Here we will consider their work pertinent to pulmonary radiotoxicology.

There are some parallels to the activities we have just reviewed at HASL. There was a large and competent industrial hygiene group, which operated for many years under the eagle eye of Harry Schulte. They had to deal not only with uranium aerosols, but with plutonium aerosols. They could tolerate much less airborne activity than in the uranium operations. Much of their early postwar work, like their MED work, concerned evaluation of possible inhalation exposures to plutonium and the prevention of further exposure. By new construction, they gradually eliminated the worst trouble spots for airborne plutonium at the laboratory, but they had to be constantly vigilant and thoroughly professional in their attack. Some typical fairly early research tied to the practical industrial hygiene problems concerned particle size studies on plutonium and uranium (Hyatt, Moss, and Schulte 1959; Moss, Hyatt, and Schulte 1961; Andersen 1964); air sampling interpretation (Schulte 1967); and the ever-present bioassay program, which we dealt with briefly in chapters 7 and 8.^(a) Later contributions in the aerosol field centered upon the concept of "respirable dust," a special problem we will take up briefly in part V of this chapter, and ever better ways to measure, interpret, and protect against airborne contamination.

In the early postwar years, Los Alamos did very little laboratory experimentation in inhalation toxicology as distinct from the industrial hygiene operations. We saw in chapter 8 that the Los Alamos staff urged that inhalation work be done but eschewed taking it on themselves. Nevertheless, Los Alamos was a strong force in the field. Wright Langham and his group did many analyses of inhalation problems and were at the center of any national or international

(a) This program, of course, concerned excretion of material usually acquired by inhalation.

meeting where airborne hazards were under discussion. It appears that the Los Alamos input had much to do with focusing attention on inhalation hazards at the continental and Pacific weapons tests. Indeed, Wright Langham was considerably involved with the development of the so-called "safety shots" carried out at the Nevada Test Site and elsewhere to evaluate the dust and aerosol hazards from small-scale area contamination with plutonium (see chapter 14). It was Wright Langham and his Los Alamos colleagues who were called upon to evaluate the surface and airborne contamination problems at Palomares, Spain and Thule, Greenland (see Stannard 1973).

Because of its closeness to the weapons program, the Los Alamos Health Division staff was immediately and deeply involved in the problems of fallout. They were concerned with aerosol and meteorological aspects as they bore on hazard evaluation and did yeoman duty along with HASL in tracking and measuring fallout. Some of the experimental work described in chapter 8 was undoubtedly stimulated by the problems of fallout from the weapons testing program.

When J. W. (Jack) Healy came to Los Alamos from Hanford, he brought with him a keen interest in environmental contamination problems and the development of suitable information on the environmental transfer of radionuclides. Among his interests has been the problem of resuspension of deposited radionuclides, especially plutonium, by wind. He and others from Los Alamos have made many field observations of these phenomena. In addition, the laboratory built a small wind tunnel to promote experimental checks of the field observations (more in chapter 15).

Despite this considerable interest, the Los Alamos Laboratory was content for many years to let others do any needed inhalation experiments involving animals or man in the laboratory. This changed markedly when the hot particle problem stimulated greatly increased and cooperative efforts to solve it. As we saw earlier in the chapter, Hanford, Lovelace, and Los Alamos were tied into a coordinated effort on various aspects of the hot particle problem (see section V A). Los Alamos attacked the problem initially without having to set up inhalation studies by using intravenous injection of microspheres, but eventually some crosschecks were necessary in situ, and Los Alamos finally began to produce aerosols of radioactive materials for experimental use.

When Bob Thomas came up to Los Alamos from Lovelace he brought with him a keen interest in not only the hot particle problem, but the habit of doing inhalation toxicology experiments in the laboratory. Many of these are of general interest, and a few will be considered here. They are a continuation of his long-standing interest in particle transport, particularly the role of the tracheobronchial lymph nodes.

At the 1974 Hanford symposium on Radiation and the Lymphatic System, Thomas (1976) presented an analysis of the uptake kinetics of relatively insoluble particles by tracheobronchial lymph nodes. He developed models for uptake and loss, including a comparison of first-order and power-function kinetics. He concluded that we need still more work to choose a "best" model.

Toward the end of the decade of the seventies, Thomas and colleagues proved that Pu-ZrO₂ particles could indeed produce respiratory-tract tumors in the Syrian Golden hamster after many years of puzzlingly negative results (see Thomas and Smith 1979a; Smith, Thomas, and Anderson 1980; Thomas, Smith, and Anderson 1980). Thomas also prepared a book on the Syrian Golden hamster as a useful laboratory animal.

Also during the decade of the 1970s, the Los Alamos group moved strongly away from their earlier interests and emphasized molecular and cellular radiobiology. Some of this interest spilled over into the inhalation work. An example is the studies by A. Stroud on chromosome aberrations. In a series of reports in the annual reviews and in published work, Stroud (1977) studied lung cells from hamsters that had small lung burdens of ^{238}Pu in plutonium-zirconium microspheres (initial burden, 130 nCi). The cultured cells, still in the excised lung, showed an 18% to 26% increase in chromosome aberrations (abnormal metaphases) and considerable depression of growth rate and mitosis. Autoradiography demonstrated many star clusters of alpha tracks. Of special interest is the fact that these changes occurred under conditions where no histological effects were seen in the lung sections, and very few lung tumors occurred. (See work by Richmond and others in the section on the hot particle problem.) Apparently, the damaged cells did not survive in general, although a few with minor damage might be transformed to precancerous forms.

Finally we should remember that the long-term follow-up of the Los Alamos plutonium workers, which we will review in chapter 16, is basically an inhalation toxicology problem, since the route of exposure was primarily by inhalation.

5. New York University, Institute of Industrial Medicine (Later Environmental Medicine)

This organization, put together just after World War II, has been an important factor in American aerosol science, toxicology, epidemiology, oncology, and environmental science. Under the decades-long leadership of Dr. Norton Nelson,^(a) a pillar in the field of occupational medicine and later of environmental medicine, the institute has grown and prospered.^(b) It has centered on chemical toxicology, chemical carcinogenesis, respiratory function, and respiratory disease with occasional forays into and a few long-term programs in the radiation field. They pioneered some important work in pulmonary radiotoxicology.

The institute began its work in the medical school buildings on First Avenue in New York City. During 1963–1964, the Anthony J. Lanza Research Laboratory for research in environmental medicine was constructed at Sterling Forest, near Tuxedo, New York, about fifty miles from the city. Most of the radioactivity and animal programs were moved or developed there. A picture of a part of this facility adorns the inside cover of each annual report from NYU and is reproduced here as figure 9.36. We show it to emphasize the arboreal surroundings possible even at NYU. Still later, the laboratory of Aerosol Technology occupied additional space in former Bellevue Hospital buildings in the city.

The institute engaged early, along with others, in studies of the clearance of radioactive dust from the human (Albert and Arnett 1955) built initially around problems of radon and thoron. They used kaolin dust mixed with thoron gas and measured the behavior of the dust by detection of the ThB with an external crystal counter. They also used metallic iron powder activated by neutrons in a reactor. They measured effective half-life, found that bronchial clearance had

(a) Dr. Arthur Upton, formerly of Oak Ridge National Laboratory and recently director of the National Cancer Institute succeeded Dr. Nelson in 1981.

(b) The Institute became the Institute of Environmental Medicine about the time fallout became a major concern.

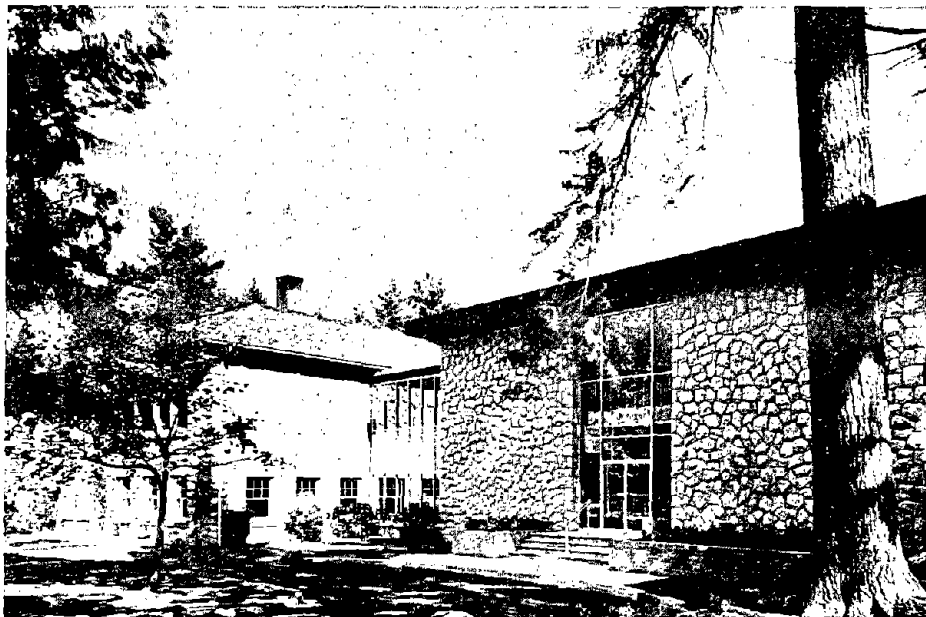


FIGURE 9.36. The Anthony J. Lanza Research Laboratories of New York University for research in environmental medicine at University Valley in Sterling Forest, New York.

two phases, and reconfirmed the finding that larger particle sizes were removed more rapidly than smaller. (Note the use of man in this and many other NYU experiments.)

This was followed by a long series of experiments on deposition and clearance (Albert et al. 1967a,b; Lippmann and Albert 1969; Lippmann 1970a). Early on, the work was done primarily to measure the kinetics of transfer of the particular radionuclide concerned. However, the convenience of using particles tagged with radioisotopes gradually shifted the emphasis to use of the radioactive aerosols as tools for measuring pulmonary function after exposure to various toxicants or during the development of respiratory disease. The convenience was enhanced by an NYU-pioneered technique of producing monodisperse insoluble aerosols that could be doubly labeled, one with ^{198}Au , the other with $^{99\text{m}}\text{Tc}$, in different size ranges (Albert and Lippmann 1968). They made over forty human inhalation tests in one year and a series of experiments with miniature donkeys.^(a) They characterized the phases of clearance and demonstrated the abnormal patterns in cigarette smokers and after pulmonary irritants. Each year saw further diversification of this methodology. In 1974, their use for diagnostic evaluations was described; in 1975 came a possible use for screening tests, etc. They had become a tool for nuclear medicine. Good bibliographies and expositions of this work occur in the annual report series from the Institute of Environmental Medicine each year.

(a) The inhalation equipment for donkeys is described by Lippmann (1970b).

Very early, the NYU group implanted radioactive sources in the lungs of rats and were among the first^(a) to demonstrate squamous metaplasia of the bronchial epithelium and squamous cell carcinoma of bronchial origin from beta radiation of the ^{106}Ru - ^{106}Rh couplet. Doses ranged from 7×10^{-3} to $14 \mu\text{Ci}$. Cancers appeared as early as eight months at doses of about 2×10^5 rad and metaplasia within six days and a dose of only 70 rad (Kuschnier et al. 1957). This report contains numerous clear examples of the histological changes seen. The work was published in 1958 (Kuschnier et al. 1958), and the dosimetry was published by Altshuler (1958). The application to airborne radioactive substances was reviewed by Nelson (1961).

Sidney Laskin, who had come to NYU from Rochester, used the implantation technique for many chemical carcinogens as well as for radioactive sources. A summary of the latter was given at the Hanford symposium in 1964 (Laskin et al. 1964) and dose-response information in 1963 (Laskin et al. 1963). They also applied their considerable expertise in aerosol science to the development of true inhalation experiments. They concentrated primarily on inhalation of chemical carcinogens, but never lost touch with the radionuclide field.

As part of work concerning radon, radon daughters, and uranium miner problems that we saw in chapter 3, Pasternak and Harley became involved in very generalized dosimetry work with alpha emitters. For reasons that are not clear from the brief expositions in the reports, they postulate the relative toxicity of thorium daughters as twenty times that of equal airborne concentrations of radon daughters, and the relative toxicity of ^{239}Pu particles as five times that of radon daughters. For the plutonium work, they tagged iron oxide particles with ^{239}Pu and measured absorption of the alpha particles in thin "tissue-like" films. This dosimetry work has concentrated on cell dose. It is continuing (see for example Cohen, Eisenbud, and Harley 1980). However, it is more a part of the radon/uranium-miner/uranium-mill problems and the material we considered in chapter 8 than the special problems of this chapter.

The NYU group was deeply involved in air pollution problems. One study that has generated much interest concerned the radioactivity in atmospheric effluents from fossil fuel power plants. Eisenbud and Petrow (1964) concluded from measurements at several power plants that a 1,000-MW coal-burning plant would discharge to the atmosphere from 28 mCi to about 1 Ci/yr of ^{226}Ra and ^{228}Ra . This is, of course, from the natural radioactive materials in the coal. A similar-sized oil-burning plant would discharge much less, about 0.5 mCi/yr. Eisenbud concludes that these quantities exceed the normal releases of fission products from comparably sized nuclear power plants.^(b) In addition, of course, the fossil fuel plant releases fly ash, SO_2 , etc.

Other facets of NYU's rather extensive program on radionuclides either do not concern inhalation problems, have already been discussed in chapters 3 and 8 (NYU 1974), or concern environmental and accidental intakes by humans, which we will review subsequently. Obviously, the contributions have been major but are spread broadly among several fields.

(a) The NYU and Pittsburgh work (see below) seems to have been done over essentially the same time period. (See section D 7.)

(b) This concerns only normal operations in both cases, not emergency releases.

6. Oak Ridge National Laboratory, Biology and Health Physics Divisions

a. Health Physics Division

During and after the war years, operational problems at the Y-12 plant at Oak Ridge often raised questions about determination of lung burdens. In some instances, specific inhalation research was requested (e.g., memo from Sapirie to Dunham 1966), but it was not intended that the research be done at Oak Ridge National Laboratory (ORNL). It was a matter of pushing the AEC to see that some of the local problems, such as high-fired oxide aerosols, were attacked by one of the inhalation laboratories. The laboratories were quite responsive. However, the Health Physics Division found it necessary to mount a few inhalation experiments of its own with uranium isotopes. These were in response to practical problems of occupational exposure in the plant, including the finding of workers with significant levels of uranium isotopes in urine samples.

Muir et al. (1959) and Fish (1961) report on inhalation of uranium aerosols by mouse, rat, dog, and man. Long-term retention of U_3O_8 was indicated in lungs and pulmonary lymph nodes, but no toxic effects were noted. The primary purpose—correlation of lung burden with urinary excretion—was met in part. The abstract of this paper conveys the substance of the results:

Six cases of accidental inhalation of uranium compounds have been studied to compare various methods of estimating body burden. One accident, involving U_3O_8 , was re-enacted and an estimate of potential lung burden was derived from air sampling data; this, along with estimates based upon blood analysis and urinalysis, compares with in vivo gamma counting results with ± 50 per cent. Two cases of uranyl nitrate inhalation were analyzed by comparing the individual uranium excretion rates with those of twelve humans given known intravenous injections, and also by collecting all of the urine for long periods of time: the estimates agree to within a factor of 2. Data obtained from these accidental exposures, along with a field study correlating air contamination parameters and uranium excretion levels for a variety of industrial jobs, have been used to fashion a tentative empirical model relating body burden to air contamination and to excretion.

Dogs exposed to a single inhalation of uranium fumes (U_3O_8) retain approximately 25 percent of the inhaled material. About half of the retained lung burden is eliminated rapidly with a biological half-life of 4-1/2 days while the remainder is cleared at a rate of half every 100 days. About 0.01 percent of the portion that is eliminated via the gastro-intestinal tract is absorbed into the bloodstream. The concentration of uranium in the tracheo-bronchial lymph nodes increases while the amount in the lungs decreases so that after about 4 months the uranium concentration in the lymph tissue exceeds that in the lung.

In vitro studies of the solubilities of U_3O_8 and uranyl nitrate in an ultra-filtrate of blood as a function of particle size have been initiated. Animal inhalation projects, now under way, are designed to simulate with mice, rats and dogs the actual exposures presented to the human subjects. Correlation of the industrial exposure data with the laboratory studies tends to support the empirical model.

(Fish 1961)

This work shows in detail the in-plant layouts for the human exposures on a case-by-case basis along with estimates of lung burden from urinalysis, blood samples, air samples, and in-vivo counting, also the change in lung burden with time—all of interest for correlation with the animal data and experience after intravenous injection in humans.

Of similar interest is a report on four cases of employees showing unusually long retention of uranium dust (West and Scott 1969). Despite diligent efforts, they could not establish completely the reasons for the unusual retention times

in these cases. Animal work at Hanford using the same material did not confirm this long retention time.

b. Biology Division

In the mid-1960s, the Biology Division entered upon a cooperative program in carcinogenesis with the National Cancer Institute. It was known as the Carcinogenesis Program of the Biology Division. This did not use radionuclides per se, so a detailed review is beyond our scope. In principle, the program was oriented toward smog problems and chemical carcinogenesis. It called for use of specific-pathogen-free mice, some of which received 100 R whole-body x-radiation and/or infection with influenza virus. They were then placed in inhalation chambers and exposed to either ozonized gasoline or an insoluble chromium oxide dust. A typical result of this program is seen in a paper by Nettesheim and colleagues given at the Oak Ridge symposium in October 1969 (Nettesheim et al. 1970). There were sex differences in effectiveness. For example, irradiation raised the incidence of lung tumors in female mice but not in males. Tumors were largely adenomas and adenocarcinomas. The combination of treatments had little in the way of additive or potentiating effects. At this same meeting, Kastenbaum urged more application of factorial experiments to the inhalation field (Kastenbaum and Mitchell 1970).

7. University of Pittsburgh Graduate School of Public Health and University of Cincinnati Kettering Laboratory

Under the influence of Theodore Hatch, long-time professor of industrial health engineering, and his colleagues, the University of Pittsburgh School of Public Health and the Industrial Hygiene Foundation of the Mellon Institute have a many-decade reputation as centers for inhalation toxicology. We were introduced to the classic text by Drinker (Harvard) and Hatch at the beginning of this chapter and noted that the first edition was published in 1936. Soon after the end of the war, Hatch's laboratory published a definitive review of particle-size effects on retention in the human lung (Brown et al. 1950) based in part on work done for the Chemical Corps, U.S. Army.^(a)

In the early 1950s, the laboratory acquired Herman Cember as a graduate student (M.S. 1952, Ph.D. 1960). Under the supervision of Ted Hatch, he became something close to a one-man show in pulmonary radiotoxicology. He studied pulmonary retention and clearance with small particles of radioisotopes; he implanted beads of ^{90}Sr in the lungs of rats; he produced bronchogenic carcinoma with ^{144}Ce fluoride insufflation; and he attacked the hot particle problem long before it became a problem. In short, he demonstrated or confirmed many of the phenomena that were more laboriously developed by the true inhalation experiments elsewhere.

It started with work on the pulmonary penetration of particles administered by intratracheal insufflation (Cember et al. 1954).^(b) They used radioactive

(a) It appears that every laboratory had its share of reviews on deposition, retention, and clearance of dust. These are not unduly repetitive. Many introduced their own experimental approaches. There are a few conflicts, but, on the whole, each adds something to the accumulated wisdom on the subject.

(b) Yes, Cember did have collaborators, but the arrangement was quite different from the large groups we have been considering heretofore in this chapter.

barium sulfate^(a) and measured particle retention and distribution by autoradiography. They concluded that about 40% of the amount intubated reached the deep respiratory tract. They did not see much pulmonary damage and were puzzled that they saw much less than Lisco and Finkel (1949) had found with ^{144}Ce oxide. A possible explanation was more general tissue distribution of the cerium oxide, which was a fume. In a later experiment with multiple injections and a longer observation period, they found extensive pulmonary damage, squamous metaplasia, and squamous cell carcinomas, even from a beta emitter of such low energy as ^{35}S (Cember and Watson 1958a).

Like many other investigators entering the pulmonary radiotoxicology field, the Pittsburgh group was surprised by the relatively rapid clearance from the lung of a substance like barium sulfate considered to be extremely insoluble *in vitro*. They turned to thallium-activated clay particles using the same montmorillonite clay adapted later by the Lovelace group (Cember, Watson, and Grucci 1957). They got longer retention and, of course, very nonuniform distribution of dose, but no biologic effects in rats over a nine-month period. The doses were not high.

Intrigued by the results of Lisco and Finkel (1949) with ^{144}Ce and pessimistic about lung cancer being caused by radioactivity because of the relative dearth of reports of lung tumor formation in either animals or man in the few studies reported through the early 1950s,^(b) Cember and colleagues gave $^{144}\text{CeF}_3$ by intratracheal insufflation at doses of 0, 5, 15, 25, and 50 μCi per rat. Bronchogenic carcinoma was observed in each group with frequencies of 1/27, 1/23, 7/28, and 4/15, respectively. The minimum tumorigenic dose was calculated as 2,400 rad.

The work with ^{90}Sr beads paralleled in concept the experiments discussed at Harvard and NYU above. The rationale came out of findings that x-ray doses to the lung were much more effective than point sources (e.g., ^{35}S) giving the same dose (Cember et al. 1954, 1955). Using a solid bead permitted more precise definition of dose and its distribution (so long as the bead remained intact) and was regarded as more uniform than the radioactive particulate source. Twenty-three rats received one radioactive bead each, twenty rats received nonradioactive beads (stable strontium-glass), and there were two types of controls. The survival patterns up to 550 days were not different between the groups receiving the radioactive beads and those receiving the nonradioactive beads. Both groups suffered from the trauma of the lung puncture. However, the group with the implanted ^{90}Sr beads produced a number of primary malignant tumors, all but one associated with the bead. There were four squamous cell carcinomas. The dose rates were from 160 to 660 rad/day and total time of the exposures hundreds of days. Hence, the total radiation dose was enormous and the effectiveness per rad much lower than the uniform x-ray dose. The experiment did prove at a time when there was not very much information that a source of radioactivity in the lung could produce lung cancer (Cember and Watson 1958b).

We have not quoted all of the pulmonary radiotoxicology work done at Pittsburgh, but we have a fair sample. Cember avoided the complexities of producing aerosols of radioactive materials and was able to cover quickly ground that the later very large experiments covered more deliberately and in greater detail (for review see Cember 1964a).

(a) The tag was ^{35}S . Clearance was measured also with mercury sulfide tagged with ^{203}Hg .

(b) How things have changed!

In 1960, Cember received his Ph.D. and moved to the famous Kettering Laboratory at the University of Cincinnati. He continued his work in pulmonary toxicology there. In 1963, he took part in the IAEA symposium on mining and milling of nuclear materials with a review on pulmonary cancer (Cember 1964b). At the Hanford symposium on Inhaled Particles and Gases he presented new results (1964a) on intratracheal injection of ^{144}Ce in rats at doses from 0.5 to 50 μCi .^(a) He found lung cancer at every level and established a dose-response relationship that was concave upward or what Dr. Cember called "the lower half of an ogive-shaped dose-response curve." The lowest dose was at about 700 rad. An average cumulative incidence frequency of about 2% was associated with this dose, but the confidence band went from below the abscissa to about 8%.

Later, Cember took on very broad teaching responsibilities, moved to Northwestern University, wrote a broadly based textbook of health physics, and went on to other things. Plaudits are due him for the number of basic areas in pulmonary radiotoxicology he was able to cover, many in a pioneering manner.

8. Wayne State University

Arthur Vorwald, a pathologist with many years of experience in pulmonary pathology at institutions like the Trudeau Sanitarium at Saranac Lake, New York, spent the war years in the U.S. Navy. There he became interested in various problems of toxic gases and high-altitude physiology. Soon after the war, he organized a center for the study of air pollution problems at the Wayne State University Medical School in Detroit. They had a variety of experiments, including one in which the air from an arterial street beside the school was piped into animal exposure chambers.

A part of the program was a study of the inhalation toxicology of the rare earth elements, a somewhat neglected area. Harry Berke, who was a part of the original Alpha Laboratory group at Rochester, joined the staff to carry on work with some of the radioactive isotopes of the rare earths, as did Donald Willard who migrated from Hanford. The basic plan was, as I recall, to compare various mixtures of stable and radioactive isotopes of rare earth elements to check on possible chemical toxicity and/or carrier effects; also to compare beta-particle effects with those of x-irradiation. We can give only an example or two of the results from this laboratory.

Berke, Wilson, and Berke (1968) and Berke and Deitch (1970) used $^{152-154}\text{Eu}$ in rats. This radioisotope has a mixture of beta and gamma emissions. They gave repetitive exposures, seven hours per day, five days per week, for twenty-four weeks. Maximum concentrations reached on this regimen were about $18 \times 10^{-3} \mu\text{Ci/g}$ whole body or $150 \times 10^{-3} \mu\text{Ci/g}$ lung. Cumulative radiation doses were about 8×10^3 rad whole body and 60×10^3 to lung.

In the 1969 paper, the authors describe changes in the ratio of large to small lymphocytes. It increased progressively in exponential relationship to cumulative exposure. Since the results paralleled those of repetitive x-irradiation, the Wayne State group felt that this ratio might be useful in internal emitter work for measuring dose equivalence.

(a) This experiment and the one reported from Pittsburgh seem almost identical. Perhaps it was an extension or a recasting of those results.

The 1970 paper concerns carcinogenesis. The rats developed severe inflammatory changes in the lungs, but no neoplasias were seen. This was just before the Lovelace work on beta-gamma emitters had reached open literature publication. The authors wondered if beta particles might not have a low tumorigenic potential. In retrospect, it appears that the doses were very large—perhaps so large that the lung pathology overwhelmed the development of cancer. Yet, in later work, cancer has appeared at beta-gamma doses in the same range or even higher. No ready explanation comes to mind.

Later the laboratory published studies of mucociliary transport rate using roentgenography and a radiopaque medium placed in the trachea of a lightly anesthetized rat (Berke and Roslinski 1971), as well as work in other areas of toxicology.

9. Other U.S. Work

The inhalation problems were sufficiently pressing and sufficiently universal that occasional experiments were done in laboratories not engaged in the mainstream or even the sidestream efforts.

Argonne National Laboratory got involved in some pulmonary studies through accidental exposures to radium (of course radium was a mainstream effort at Argonne). Marinelli and Gustafson (1952) and Marinelli et al. (1953, 1958) measured the transport of radium sulfate from the lung as well as its excretion. They found sharp localization of the deposits in lung and individual differences in elimination. The average half-life in the thorax was 120 days in the first year.

Miller and Corcoran (1958) applied their newly developed whole-body counter to estimate very long-term retention (2,300 days) of radium, and Marinelli et al. (1958) obtained information on excretion as well as retention over long periods after an accidental inhalation.

Much later, Rundo and Sedlet (1973) studied retention and elimination of ^{249}Bk - ^{249}Cf following an acute accidental inhalation.

Paul Ziemer's laboratory at Purdue suddenly did some work with europium (Johnson and Ziemer 1971). Results were of interest in that, among other things, whole-body retention could be described equally well by two mathematical models, a dual-term exponential or a power function of time. This work was tied into a general interest at the laboratory in the biological effects of the rare earths.

There are undoubtedly isolated pieces of U.S. work that have been missed. Nevertheless, the quantity and quality of material we have now reviewed in this chapter and in chapters 2 and 3 should be enough to convince anyone that the United States mounted more than adequate programs to deal experimentally with the problems of inhaled radioactive materials.

10. Work Abroad

Space limitations and the scope for this book permit only the briefest consideration of work abroad, except where the early history took place largely in other countries. France and the Soviet Union have conducted the most extensive experimental programs in pulmonary radiotoxicology. Despite outstanding work in aerosol science and major contributions to internal emitter toxicology in Great Britain, the two did not join forces very often in experimental work. In pulmonary radiotoxicology, the United Kingdom has acted more as a coordinator and reviewer of the problems and their interpretation than a developer of

new information, with some notable exceptions. Japan began inhalation studies on plutonium and fission products when their reactor program began to develop. There is an alpha emitter facility at the National Institute of Radiological Sciences in Chiba City patterned in part after Rochester's Alpha Laboratory, and Pacific Northwest Laboratory. West Germany has produced several key studies (see chapter 3). Workers in Finland and Eastern Europe have exhibited considerable interest and done significant but not numerous experimental studies.

Since space prohibits even a listing of key papers, it is suggested that the literature be pursued by reference to one or more of the reviews cited in this chapter, as well as the specific citations concerning radon and uranium mining problems in chapter 3. Especially helpful would be the reviews by Bair and colleagues in the *Handbook of Experimental Pharmacology*, Vol. 36 (Bair et al. 1973); the several publications of the IAEA, especially *Radiological Health and Safety in Mining and Milling of Nuclear Materials*; ICRP Publication 31 (1980); the several translations of *Doklady Biophysics* and the Moskalev Monograph (1966) translated by the U.S. AEC; the series of books from the USSR on specific elements edited by Letavet and Kurlyandskaya (1962–1970) and translated by Dolphin (Pergamon Press); the Hanford symposia, especially the one on Inhaled Particles and Gases in 1964; and the publications of the United Nations Scientific Committee on Effects of Atomic Radiation (UNSCEAR).^(a)

Individuals and institutions frequently cited, and thus ones to be watched for especially, are:

Austria: Pohl and Pohl-Rüling
 Belgium: Dautrebande
 Finland: Miettinen
 France: Commissariat à l'Energie Atomique, Fontenay-aux-Roses—Chameaud, Perraud, Lafuma, Masse, Metivier, Morin, Nénot, Nolibé
 Japan: National Institute of Radiological Sciences—Suzuki, Matsuoka.
 Great Britain: Medical Research Council, National Radiological Protection Board, United Kingdom Atomic Energy Committee, University of Newcastle upon Tyne—Clarke, Dolphin, Eve, Mayneord, Smith, Stewart, Thorne, Vennart, James, Stradling
 Federal Republic of Germany: Feinendegen, Hug, Jacobi, Schmidke
 Yugoslavia: Djurić
 Soviet Union: Buldakov, Burykina, Lyupchanskii, Kurlyandskaya, Lemberg, Moskalev, Nifatov
 Sweden: Walinder

V. Special Problems

Most of the work in pulmonary radiotoxicology, both in the MED days and in the postwar era, was based on operational problems, either encountered or anticipated. There were a few special problems that attracted the attention of every laboratory in the field and others that were best attacked by interlaboratory groups brought into focus by administration. Some of these stimulated significant new research efforts, particularly in the early postwar era. Others required primarily application of knowledge already gained. They are best discussed as entities and are brought together in this section.

(a) Remember that work primarily on radon and uranium mining was cited in chapter 3.

A. The Hot Particle Problem

Honors for being the most diversionary, most divisive, and most expensive go to the so-called "hot particle" problem. Simply stated, this revolves around the question as to whether or not a small discrete source of radiation in the lung is uniquely carcinogenic. This is nothing new. It had been fully recognized in the early work with both lung and bone, but was presented in a sensational manner.

This is part of a dilemma that has for many decades dogged the footsteps of both those devising regulatory standards and those interested in basic problems of internal dosimetry. It has been known ever since the first autoradiographs showed that deposited radionuclides either entered the body in aggregated form or became aggregated *in vivo*. Especially serious attention was devoted to this phenomenon by those working with bone and bone-seeking elements. We have seen numerous instances of the phenomena themselves in earlier chapters and in earlier parts of this chapter. Investigators in the inhalation field have mused for years on the question of the relative effectiveness of the same total dose to lung received in different patterns. Hot particles were noted at Hanford and at Oak Ridge in the 1940s (Morgan 1948). They called them "specks" then.

However, the hot particle problem we are discussing arose suddenly in 1974. An organization known as the Natural Resources Defense Council (NRDC) produced an analysis that concluded, partly by logic, partly by assumption, that hot particles (i.e., radioactively "hot") were uniquely carcinogenic and that the current maximum permissible lung content of ^{239}Pu was 115,000 times too high^(a) (Tamplin and Cochran 1974). This was followed by an official petition to both AEC and the U.S. Environmental Protection Agency (EPA) for a 115,000-fold reduction in radiation standards applicable to plutonium and other actinides.

The back-up material for the petition made use of many of the experimental results we have already reviewed. It also brought in some evidence from the external radiation field. The story has been told very well in many places and many times. Probably the most complete factually are the reviews by Bair, Richmond, and Wachholz (1974); Richmond (1975, 1976); Healy, Richmond, and Anderson (1974); NCRP (1975a); NAS-NRC (1976); and Part G of ICRP Publication 31 (ICRP 1980). Nevertheless, we must review the story briefly because of its role in pulmonary radiotoxicology and in order to appreciate the new research and analyses of old research stimulated by this event.

The impact of the NRDC report and petition was enormous. The low-level radiation controversy was in a phase of logarithmic growth. The LMFBR program, which could produce potentially very large quantities of plutonium, was being pushed by AEC. Environmental Impact Statements were being written for everything, and the one for the LMFBR received considerable attention with numerous hearings. There was much opposition to manufacturing more plutonium. The Congress and executive branches of the U.S. government jumped in vigorously. The public was upset and astonished to hear that the standards whose credibility was already being eroded might be off by such an enormous factor. Blue-ribbon committees were appointed both within and outside of government, on both sides of the Atlantic, to examine the situation and make recommendations. The AEC encouraged its laboratories to undertake some

(a) Note that they were so sure of themselves they did not round the number off to 100,000 or simply 10^5 .

critical experiments that might fill in some of the important gaps in our knowledge. Investigators who felt their results had been misinterpreted or misused produced statements and/or went back to do more experiments.

A brief review of the original premises and what happened later follows.

1. The Proposition

The hot particle proposition as enunciated by NRDC contains, among others, the following basic premises and ideas:

- a. It is well known that plutonium and other actinides, particularly in their insoluble forms, deposit and remain in lungs in the form of particles. These particles disappear very slowly.
- b. The dose rate around such particles can be extremely high and presents a unique hazard for the production of lung cancer.
- c. Plutonium is one of the most potent carcinogens known.
- d. The assumption of average dose to lung as the pertinent one for cancer production is incorrect.
- e. The work of Dr. Roy Albert^(a) at NYU using rat skin exposed to electron and later alpha-particle radiation, showed that sensitive target cells resided in hair follicles about 0.3 mm below the surface of rat skin. Radiation focused into the hair follicles was very effective in producing skin cancer. In other words, there were small foci of considerably elevated sensitivity. The NRDC used this work to back its argument.
- f. This and correlations from it were termed the "Geesaman hypothesis," which stated that a sufficiently high dose to a critical architectural unit carried chances of cancer induction of 10^{-3} to 10^{-4} *per unit*. It had appeared in a report from the University of California Radiation Laboratory some years before the NRDC report was written (Geesaman 1968).
- g. Work of Bair et al. indicated the high potential for lung cancer in dogs receiving plutonium. It was postulated that this applied also to humans. Furthermore, a summary by Sanders, Thompson, and Bair (1970) concluded that nonuniform radiation (a point source) was more carcinogenic than a uniform radiation dose from an external source. They also presented a model showing increased estimated incidence of lung cancer with increasing particle size.^(b)
- h. A minute lesion in the hand of a plutonium worker caused by an imbedded plutonium particle became cancerous. (The particle had been removed by surgery soon after the incident.)
- i. A freight handler who handled a crate containing a leaking carboy of a plutonium solution received contamination of the hands, which led subsequently, according to Gofman and Tamplin, to soft tissue sarcoma on the left palm, which produced his death.
- j. The work of Laskin on imbedded sources in the lung had demonstrated production of lung cancer at doses as low as 1,400 rad.

(a) For references, see, for example, Bair, Richmond, and Wachholz (1974).

(b) This review was based upon early data, most of which involved intratracheal administration or the implantation of radioactive particles, beads, or similar sources. See subsequent and earlier sections for results of inhalation exposures.

- k. Exposures of humans to hot particles were already occurring at Rocky Flats, had occurred at Los Alamos, and elsewhere.

Out of all of this and more, Tamplin and Cochran decided that certain criteria of activity and dose rate were required to initiate the hot particle reaction. They defined a hot particle as one that presented a risk of cancer induction between $1/1,000$ and $1/10,000$. They chose to use a $1/2,000$ risk per particle. Meeting this criterion would be ^{239}Pu particles containing 0.07 pCi or more of activity. Such a particle would deliver $1,000$ rem per year or more, the "threshold" dose rate. The limit for occupational exposure should be 0.14 pCi or two of the standard hot particles.

It should be noted that the hypothesis allows for plutonium being in a form other than hot particles and implies a threshold-type response.

2. Some Immediate Responses

There were some immediate rebuttals and comments on these postulates, as follows:

- a. Albert was quick to point out that for a tumor to occur he had to include the whole hair follicle, a much larger area than that around a hot particle as defined. In fact, using focal alpha radiation he found it impossible to induce skin cancer no matter what the dose if smaller volumes were irradiated. Also, Albert pointed out that tissue damage and carcinogenicity are by no means parallel. (The chronic irritation theory of carcinogenesis, enunciated by Virchow in 1863, is no longer tenable.) There is little relation in a general sense between degree of tissue damage and cancer induction. The rat skin experiments actually showed protection for low-LET radiation when a sieve pattern replaced irradiation of the full area. Finally, the phenomenon could not be produced in other species.
- b. The enormous doses around hot particles would be more likely to kill surrounding cells than to transform them to precancerous cells.
- c. Inhaled material is constantly moving around in the lung. Only when fixed in scar tissue would a hot particle remain as a fixed source.
- d. Phagocytosis and other processes result in aggregates of material no matter in what form it enters. The entry form governs only the initial behavior.
- e. Bair and colleagues pointed out that the differences they had found between different forms of plutonium and different particle sizes were far smaller than the postulates of the hot particle hypothesis required and applied more to one experiment than to another, i.e., it was not established yet as a universal phenomenon despite the model proposed in 1970.
- f. The pathologists termed the lesion in the hand of the plutonium worker only precancerous and not clearly related to the previously imbedded particle. The cancer of the freight handler was not clearly due to the small radiation exposure incurred.
- g. Alpha-particle irradiation does not usually exhibit a threshold-type response.
- h. The hypothesis as stated has many problems of logic. An example is that the risk from a particle of approximately 0.1 pCi of plutonium would be decreased by a factor of over $100,000$ if the particle were to break into two equal halves.
- i. he exposed plutonium workers at Rocky Flats and Los Alamos already had many more hot particles than two. In fact, nearly everyone does. Many

cases of lung cancer should have appeared over the long periods (over thirty years now in some cases) if the risk were 1/2,000 per particle. To date, not a single case of lung cancer or other cancer clearly associated with radiation has appeared in these workers, despite diligent examinations and follow-ups: (There are those who say these analyses are faulty, e.g., Martell.)

Some of these ideas appeared in hearings on the LMFBR held by the EPA. Some appeared in reports of expert committees convened to examine the problems. Among these are reports of the U.S. National Academy of Sciences—National Research Council (NAS-NRC 1976), U.S. National Council on Radiation Protection and Measurements (NCRP 1975a), The Biophysical Society (1974), and the U.K. National Radiological Protection Board (Dolphin 1974). Specific reviews came from individual laboratories also (e.g., Healy, Richmond, and Anderson 1974; Richmond 1975, 1976), and a full review was done by Bair, Richmond, and Wachholz (1974) as an AEC report.

The NRDC issued critiques of some of these documents. These appeared as NRDC reports, sometimes as part of the hearings process on the LMFBR.

The many reports examining the NRDC report and proposal were uniformly negative in essence. Some objected to the whole idea, others felt a service had been rendered by highlighting the problem, but that the petition had gone much too far. Many called for more research. All agreed we did not have good evidence that particulate sources were more carcinogenic than discrete sources.^(a)

Enough about the polemic. It is the research associated with or pertinent to this polemic that is our primary interest here. The balance of our discussion will review work done wholly or in part in response to these problems. Much of it was clearly in progress before 1974, but it was accelerated and expanded by the hot particle controversy.

3. Contemporary Experimental Work Pertinent to the Hot Particle Proposal

a. Experimental Approach

The work most obviously directed at the hot particle problem took place at Los Alamos. They wanted to check on the effects of fixed sources but to avoid the trauma associated with implanting beads and wires. Richmond, Langham, and Stone (1970) investigated the effects of $^{238}\text{PuO}_2$ particles lodged in lung vasculature after intravenous injection. There was a small microlesion around the particle with complete degeneration of the cells close to the particle, but no cancer-like changes.

The Los Alamos group then turned to the use of microspheres. These inert particles, developed by the Nuclear Products for Medicine branch of the 3M Company, were already in use for clinical and therapeutic applications in nuclear medicine. They were available in a variety of controlled sizes and could

(a) Several of the analyses did review the few experiments already done that addressed specifically and in a controlled manner the question of discrete versus diffuse radiation sources. Many of these were, like Albert's work, concerned with effects in skin (e.g., plaques of P-32). The evidence indicated that the more uniform source was the more damaging in general. (The pertinent experiments are cited in the references already given.)

be treated to carry varying amounts of radioactivity. By selecting a size that would be caught in the smaller blood vessels of the lung, a static source could be produced by intravenous injection of such microspheres. The animal chosen was the Syrian hamster for the reasons given in section IV. The nominal levels, specific activity, equivalent diameter of pure $^{238}\text{PuO}_2$, and the PuO_2 weight fraction in their early experiments are given by Richmond, Langham, and Stone (1970, table 7). There were in toto over 150 hot particle experiments carried out at Los Alamos.^(a)

As the experiments progressed, the investigators were surprised at the lack of biological effects. Animals taken by serial sacrifice showed minor changes around the source, and, as the levels were increased, some radiation pneumonitis. Lung tumors or even metaplasia were of conspicuously low incidence. In approximately 1,150 hamsters living their full life spans with about six million microspheres with specific activities above 0.07 pCi each, only three primary lung tumors occurred. The associated tumor risk was calculated to be about 10^{-7} per particle instead of the 10^{-3} of the Geesaman hypothesis. Is the hamster unusually resistant to lung tumor formation? We have already seen that Little at Harvard easily produced lung tumors in the same species and strain of animals with instilled ^{210}Po . Also, chemical carcinogens are quite efficient in producing lung cancer in the hamster.

The Los Alamos people turned to plutonium-zirconium oxide microspheres, which could be made of exceptionally uniform particle size,^(b) even more uniform than the 3M microspheres. Also, ceramic zirconium oxide is chemically and biologically inert. The microspheres could be made in the laboratory (Anderson and Perrings 1978). The behavior of these, the excretion of plutonium so injected, survival, and pathological changes are given in progression by Anderson et al. (1974), Smith et al. (1976), Thomas and Smith (1979a), and in each Los Alamos annual report of the era. The negative results for life-span and biological changes, including tumorigenicity, continued so long as the number of microspheres per animal remained low enough to irradiate less than 20% of the lung mass.

If enough microspheres were crowded in to irradiate significant areas of the lung (i.e., over 20%), then lung tumor incidence began to rise. Also, intratracheal administration of a ^{210}Po solution à la Little brought incidences approaching 50%. This showed that there was nothing strangely different about the lung cancer susceptibility of the hamsters used in the Los Alamos experiments. An excellent summary table of the entire Los Alamos hot particle effort (except inhalation experiments) is given in the 1977 Los Alamos Annual Report (Anderson et al. 1978) and in ICRP Publication 31.

When the Pu-ZrO_2 was given as aerosol particles by inhalation, either in addition to or instead of injection, doses that had produced little or no effect when delivered by the entrapped microspheres produced shortening of life span, pulmonary neoplasms, and nonneoplastic pulmonary lesions (Thomas and

(a) There was a series of papers in *Health Physics* from Richmond's group, all under the basic title, "Biological Response to Small Discrete Highly Radioactive Sources." The one in 1970 cited is more closely related to reactions of the lung.

(b) The radioactivity of a uniformly loaded microsphere varies as the cube of the radius. For example, a 9% variation in dose rate can result from only a 3% change in particle diameter.

Smith 1979b). The results of this inhalation work are shown in table 9.17A, B. The dosages and treatment patterns are given in table 9.18.

TABLE 9.17. Results of Inhalation Studies with Syrian Hamsters Receiving (Pu-Zr)O₂

A. Pulmonary Neoplasms

Group	No. of Tumor Bearing Animals/ No. of Animals	No. with Multiple Tumors/ No. with Tumors	Adenoma	Adeno-carcinoma	Squamous-cell Carcinoma
A	1/53 (2%)	0/1 (0%)	1/1 (100%)	—	—
B	5/43 (12%)	0/5 (0%)	5/5 (100%)	—	—
C	2/40 (5%)	0/2 (0%)	2/2 (100%)	—	—
D	0/45 (0%)	—	—	—	—
E	1/55 (2%)	0/1 (0%)	1/1 (100%)	—	—
F	0/44 (0%)	—	—	—	—
G	20/50 (40%)	4/20 (20%)	12/20 (60%)	8/20 (40%)	—
H	17/60 (28%)	3/17 (18%)	11/17 (65%)	6/17 (35%)	—
I	22/44 (50%)	4/22 (18%)	10/22 (45%)	9/22 (41%)	3/22 (14%)
J	0/45 (0%)	—	—	—	—

B. Non-Neoplastic Pulmonary Lesions¹

Group	Fibrosis	Bronchiolar Adenomatoid Lesions (BAL)	Squamous Metaplasia
A	5/52 (10%)	24/52 (46%)	1/52 (2%)
B	3/38 (8%)	4/38 (11%)	—
C	1/38 (3%)	7/38 (18%)	1/38 (3%)
D	—	1/45 (2%)	—
E	—	5/44 (11%)	1/44 (2%)
F	2/44 (5%)	5/44 (11%)	1/44 (2%)
G	24/30 (80%)	18/30 (60%)	4/30 (13%)
H	16/43 (37%)	11/43 (26%)	1/43 (2%)
I	17/22 (77%)	12/22 (55%)	2/22 (9%)
J	—	1/45 (2%)	—

¹In non-tumor-bearing animals

Source: Modified slightly from Thomas and Smith 1979a.

Note: For dosages and sequences see Table 9.18.

It should not be said that there was absolutely no effect in the intravenous experiments. Bronchioadenomatoid lesions (BAL) appeared at low incidence, and two animals receiving two thousand microspheres with a lung burden of 0.84 nCi developed tumors. Yet, the group with the highest incidence of BAL, viz., 6% that received six thousand microspheres for a lung burden of 26 nCi, did not develop a single primary lung tumor (Smith et al. 1976). It appears that disturbances began, but they never went on to the extent seen with the more diffuse sources.

TABLE 9.18. Experimental Design for Studies with (Pu-Zr)O₂ Injected I.V. into or Inhaled by Syrian Hamsters

Group ID	No. of Hamsters		Radio-nuclide	Mean No. of Spheres Injected	Mean Initial Pu Lung Burdens (nCi) ¹		Median Lifespan (Days post exposure)	
	Male	Female			Injection	Inhalation	Males	Females
A	26	27	²³⁹ Pu	~60,000	117	0	399	386
B	17	26	²³⁹ Pu	0	0	8	467	393
C	16	24	²³⁹ Pu	~30,000	49	6	538	236
D ²	23	22	—	~30,000	0	0	532	368
E	34	21	—	0	0	0	547	239
F ³	23	21	—	0	0	0	582	357
G	23	27	²³⁸ Pu	~20,000	56	87	198	234
H	30	30	²³⁸ Pu	~20,000	53	76	268	252
I	20	24	²³⁸ Pu	0	0	101	176	171
J	14	31	—	0	0	0	447	445

¹Estimated from long-term lung retention kinetics (alveolar burden). The two digits used in these numbers were determined from retention equations, but it is obvious from such techniques that rounding off is a sufficiently accurate accounting of the actual lung burdens (e.g., 87 nCi could as accurately be reported as 90 nCi).

²Group D received ⁵⁷Co labelled ZrO₂ and i.v. aerosol particles.

³Group F received unlabelled ZrO₂ aerosol particles.

Source: Reset from Thomas and Smith 1979a.

The conclusion from this Los Alamos work strongly favors the thesis that diffuse sources^(a) are considerably more effective than a fixed concentrated source.

The original NRDC report quoted as strong evidence favoring the hot particle hypothesis the work of both Cember and the NYU group on implanted sources. This is to a degree a non sequitur. The experiments involved very large doses, as we have seen. One interesting report of Cember's was not quoted. This was work comparing the efficiency of radiation from insufflated barium sulfate labeled with ³⁵S (see section IV) and external radiation from x rays. There was a wide range of doses. The endpoint was survival, not cancer induction. The x-ray effects were much larger for a given total dose. Cember concludes, "The dramatic results of the external pulmonary irradiation indicates the validity of the hypothesis that a spatial concentration of absorbed energy may be less hazardous than a more uniform distribution of the total amount of absorbed energy in a greater volume of tissue" (Cember, Watson, and Grucci 1956, p. 400).

Meanwhile, across the country at Harvard, Little and colleagues were adding interesting new information to that already reviewed in section IV. They administered ²¹⁰Po intratracheally to hamsters in a relatively soluble form (saline solution) and when carried on iron oxide particles, i.e., as a nonuniform "hot spot."

(a) With the understanding that "diffuse" is used in a relative sense. Probably none of the sources were really uniformly distributed.

With doses from 55 to 2,700 rad to whole lung, the tumor yields from the particulate sources were equal to or less than those from the "uniform" exposure.^(a) This experiment was done specifically in response to the hot particle problem (Little, Kennedy, and McGandy 1978). In the next year, the same laboratory concluded that dose rate had little influence on carcinogenicity in this system (Little and Kennedy 1979). The pathogenesis, possible cells of origin of the tumor, and mechanistic aspects were added to the study, but they do not pertain directly to our consideration here of hot particles.

In section IV, we presented the plan of the Inhalation Toxicology Research Institute's program with monodisperse aerosols of plutonium and reproduced a figure showing calculated dose relationships with particles of different levels of radioactivity. We elected to defer further consideration of this work to this section on hot particles because of its pertinence thereto.

The first experiment involves comparison of the results on inhalation^(b) of a monodisperse aerosol of $^{238}\text{PuO}_2$ of 1.5- μm aerodynamic diameter (AD) with one of 3.0- μm AD. There were some differences in retention kinetics; e.g., the retention half-times in lung were 650 days versus 440, in liver 130 days versus 140, and in skeleton 140 days versus 340 for 1.5- versus 3.0- μm AD particles, respectively. The differences reside largely in the handling of the material prior to 100 days. (These differences between particles only a factor of two apart in average diameter introduce another factor into any consideration of the long-term effects of different particle sizes, i.e., differences in tissue retention times.)

Nevertheless, the biological results to date in this Lovelace experiment do not indicate that the difference in particle size has influenced the incidence or the type of lesions seen. The work is still in progress with many animals still alive.

In a larger experiment with $^{239}\text{PuO}_2$, monodisperse particles of 0.75 μm , 1.5 μm , and 3.0 μm were inhaled. The results are somewhat less far along than the ^{238}Pu study but indicate comparable findings.

The differences between ^{238}Pu and ^{239}Pu on a microcurie basis have been suggested by some to be due possibly to the greater uniformity of dose distribution in the lungs for ^{238}Pu (Sanders, Craig, and Smith 1974).

Experiments in Lafuma's laboratory in France, using rats (e.g., Lafuma et al. 1974; Lafuma 1978), suggest that toxicity increases as the uniformity of the pulmonary distribution of the element increases. For example, ^{244}Cm was the most toxic and the most highly dispersed.

This can be illustrated by a report from the German Commission on Radiation Protection, which was requested to address the hot particle problem. The results were published in 1978 (Commission on Radiation Protection 1978). Their analysis includes most of the Russian and French work, as well as that from the United States and concludes that the more uniform doses are more hazardous. They show a "relative heterogeneity factor" and a "relative toxicity factor" for a number of actinides as derived by Lafuma. Each is relative to ^{244}Cm nitrate. There is an inverse relationship between the two as shown in table 9.19.

The toxicity factor is corrected for the different alpha-particle energies of the radionuclides involved. The range is not great, especially in comparison to the

(a) Little et al. call it uniform without quotes. I have added quotes since there were probably some particles present in both instances as polonium colloids. The iron oxide particles were, however, much larger and much less uniform than the polonium given in a saline solution (Little, Grossman, and O'Toole 1973).

(b) Note that much of the other work is not by inhalation.

TABLE 9.19. Relative Heterogeneity Factor (H) and Relative Toxicity (T) of Inhaled Actinide Compounds in Rats

Compound	H ^a	T ^a
²⁴⁴ Cm-Nitrate	1	1
²³⁸ Pu-Oxide	1.5	0.7
²³⁸ Pu-Nitrate	2.0	0.5
²⁴¹ Am-Nitrate	2.3	0.4
²⁴¹ Am-Oxide	3	0.3
²³⁹ Pu-Nitrate	5	0.2
²³⁹ Pu-Oxide	5.5	0.2

^aIn relation to ²⁴⁴Cm-Nitrate

Source: Reset from Commission on Radiation Protection 1978.

enormous differences suggested by the hot particle hypothesis, but they are reasonably regular and, of course, in the opposite direction from the postulates of the hot particle proposition.

2. Theoretical and Computational Approach

Using the principles of microdosimetry, especially the characteristics of the alpha particle track, several theoretical (e.g., modeling) approaches have been made. Early among these was work from Los Alamos by Dean and Langham (1969) and models in the NAS-NRC 1961 (BEAR) report.^(a) The former predicted that there would be an optimal dose and/or dose rate for tumor induction. The NCRP report (NCRP 1975a) contained estimates of the number of cells traversed as a function of activity of ²³⁹PuO₂ particles or uniformly distributed sources and gives numbers of singly versus multiply traversed cells for the particular source. This in turn allows calculation of the "specific energy" deposited in a microscopic area. If one makes assumptions about number of cells that must be involved (and how) in carcinogenesis, predictions can be made about incidence as a function of particle size. (This was not done in the NCRP report itself, but was engaged in by some members of the committee.)

The Los Alamos people, in designing their experiments, calculated the activity and number of ²³⁹PuO₂ or ²³⁸PuO₂ particles as a function of geometric diameter and the number of particles needed to produce one maximum permissible lung burden of 16 nCi (Richmond 1975). It would take 5.4×10^4 particles of 1 μm in diameter, but 5.4×10^{10} particles of 0.01 μm diameter to reach 16 nCi of ²³⁹Pu in the lung. They also calculated the number of cells at risk for a static lung burden of 16 nCi at the different particle diameters. With particles as large as 1 μm , only about 0.03% of the lung mass (3.6×10^8 cells) is at risk, while for the same activity, viz., 16 nCi, about 30% of the lung mass (3×10^{11} cells) is at risk with the smaller particles. Thus, the larger the particle the lower the number of cells at risk, but the higher the activity per particle. Again, it would not be surprising if there were some tradeoffs and a point of greatest hazard. Until we know more about carcinogenesis, we can only conjecture.

(a) See chapter 16.

There are also calculations of particle movement and its effect on the micro-distribution of alpha energy (NCRP 1975a; ICRP 1980, p. 87).

Mayneord and Clarke (1976) in the United Kingdom examined the hot particle problem in terms of numbers of irradiated cells and doses received. They produced a very broad study, which included linear and nonlinear dose response functions and alpha, beta, and gamma activity in point sources compared to uniform irradiation. Using an entity for expectation of effect called "absolute expectation," they calculated that in a large number of instances the mean organ dose and the assumption of a linear nonthreshold response function give a good upper limit of the expectation predicted from many of the point source postulates. This work was backed up by a detailed mathematical investigation published in a report of the U.K. Central Electricity Generating Board.

Some of the testimony at the hearings called by EPA on the LMFBR contained models and calculations of the sort we have been looking at. Since they do not introduce anything new, they will not be reviewed here. However, the reader will find these hearings a rich source of concentrated information (in places, at least).

A very simple but seldom emphasized aspect of the problem concerns the method of expressing dose. The biological data from which we derive risk estimates or other expressions of cancer incidence have conventionally used doses calculated on the basis of large volumes, i.e., whole lung, bronchial epithelium, postulated most sensitive cells or tissues, etc. If we accept the hot particle hypothesis, the calculated doses associated with a given effect would be much higher. The effect of reducing the critical volume from an average to lung to only 0.1% of the lung mass reduces the apparent effectiveness of plutonium alpha particles by a factor of 1,000. This is shown in figure 9.37, taken from Stannard (1975).^(a)

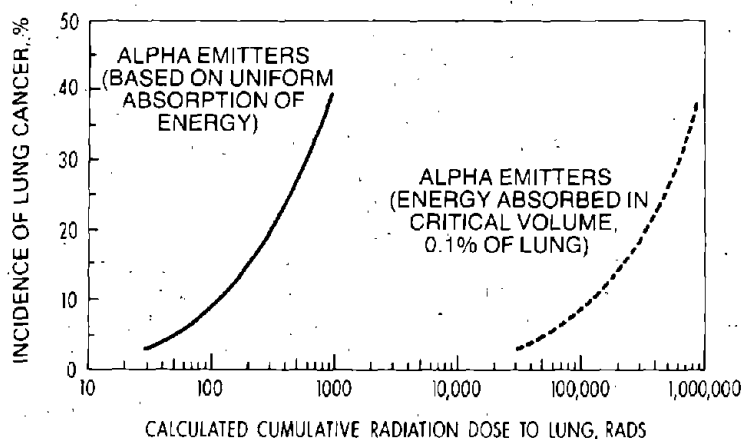


FIGURE 9.37. Illustration of effect of change in assumed tissue volume on position of dose response curve for incidence of lung cancer. (Redrawn from Stannard 1975.)

(a) A modified form of this graph appeared in WASH-1320 (Bair, Richmond, and Wachholz 1974).

This simplistic exercise points up an important fact. Both sides of these relationships should be based on the same system. We should not use macrodosimetry for determining dose associated with incidence obtained from biological data and microdosimetry for predicting incidence associated with a dose. Only if it is clear that the original incidence data and the predicted effects data utilize the same system are we playing fair. It is not fair to mix the computational approaches in midstream.

Finally, in section G of ICRP Publication 31, the task group calculated the expected number of lethal lung cancers in the dog experiments using the data on plutonium in dogs and the NAS-NRC (1976) estimates of how many 0.07-pCi and also how many 0.6-pCi particles there would be in the pulmonary region of dogs receiving the doses given. (They are 1.3 million and 200,000, respectively.) Using the proposition that a 0.07-pCi hot particle has a 1/2,000 chance of producing lung cancer, there should have been 650 lethal lung cancers *per dog* during the 11.5-yr average life span after exposure, or 100 lethal lung cancers per dog if the critical activity of a hot particle were raised to 0.6 pCi. The average dog actually had 1.9 primary pulmonary cancers.

Commentary on the Hot Particle Controversy. There seems to be little theoretical or experimental justification for the hot particle proposition as originally enunciated or as modified. The risk factor was derived almost gratuitously. The specifics have not held up. In a sense, the strong reaction of the scientific community and of administration can be viewed as a costly blunder, which derailed other important work. As in the case of the uranium miners (see chapter 3), the data were essentially already in place to tell us the correct answer. However, few knew it was in place and few believed we had enough information. Indeed, we probably did not have enough for all purposes and never will until we have a complete theory of carcinogenesis. The net result has been some progress in pertinent research and more understanding of lung dosimetry. The loss in other realms is not so easy to write off. Only in the future can we expect to answer that question.

Both ICRP and NCRP have agreed on again and reiterated the validity of using whole organs or significant radiosensitive parts of organs in calculating dose from deposited radionuclides. Yet, the problem for lung is still not settled. We are still in a quandary over many aspects of lung dosimetry and need new research. At the 1982 meeting of the Radiation Research Society, there was a special workshop, in two sessions, on lung dosimetry. One paper, by D. R. Fisher (Battelle, Pacific Northwest Laboratories) was entitled "In Search of the Relevant Lung Dose." The round table discussion, chaired by P. E. Morrow, was entitled "What is the Relevant Lung Dose?" (Fisher 1983). Need we say more?

B. Tobacco Smoke

We have seen experiments and discussions involving tobacco smoke, especially cigarette smoke, in several different contexts. Because of interest in the subject and for the convenience of the reader, a short recapitulation and a few additional observations are brought together here around the problems of pulmonary radiotoxicology.

There are at least three distinct ways in which tobacco smoke has been linked to problems in this field:

1. as a co-carcinogen with a radioactive material

2. as influencing the clearance of radioactive dust from the respiratory system
3. as the primary cause of lung cancer by virtue of the natural radioactivity of tobacco.

We will consider each of these in turn.

In reviewing the uranium miner problem (chapter 3), we saw the repeated introduction of the role of cigarette smoking as a complicating factor, i.e., as a possible co-carcinogen. The oft-repeated statement that only uranium miners who smoked got lung cancer seems to have been negated in recent years. Nevertheless, the epidemiology is still complicated by the relatively small size of the nonsmoking miner group.

The cell type in sputum samples from miners developing lung cancer in recent years has appeared to be more like that seen in smokers developing lung cancer than in the older miner population. This has led some to consider that the new cancers appearing in the uranium miner group are linked only to smoking, not exposure to radon and daughters. The marked reductions in radon levels in the mines by increased ventilation over the last decade or more support this thought. On the other hand, the current experience in no way answers the question of the role cigarette smoking played in the earlier incidence figures. Nor do differences in the smoking habits of different populations clinch the idea. Other factors are different too in these populations.

The animal work at PNL in which cigarette smoke was added to radon and daughter products (see chapter 3, section VIII B-2) went in the opposite direction. The presence of cigarette smoke seemed to mitigate the effects of radon and daughters. The authors speculate that the smoke increased the thickness of the mucus layer and/or stimulated mucociliary clearance. The PNL work with smoking dogs concentrated more on lung clearance than influence on cancer incidence.

Albert et al. (1975) used the NYU technique of double tagging of aerosols (see section IV) to measure short-term effects of cigarette smoking on bronchial clearance in humans. They could establish a base-line clearance rate over several hours by measuring the rate of removal of an aerosol tagged with one radionuclide (e.g., ^{198}Au or $^{99\text{m}}\text{Tc}$). With the base line established, a second aerosol marked with the other tag could be inhaled and this followed quickly by the smoking of several cigarettes. The clearance of the second aerosol was then measured. They continued measurements up to 90% of the total clearance. With fifteen subjects, the smoking episode increased clearance rate by a factor of about two. The effect was consistent. However, the authors quote work from other laboratories that showed slowing of bronchial clearance in some cases, acceleration in others.

Further NYU work with the donkey showed slowing of clearance after more than fifteen cigarettes.

Examination of the chronic effects of smoking has tended toward finding slowed clearance rates.

Many years before the NYU work, Bair and Dilley (1967) at Hanford found no influence of cigarette smoke on clearance of $^{59}\text{Fe}_2\text{O}_3$ or $^{51}\text{Cr}_2\text{O}_3$ particles from the lungs of rats. These were acute exposures. The same results appeared in dogs that smoked twenty cigarettes per day for five days per week for over a year. In later work on plutonium clearance quoted earlier in this chapter (section IV, part A 4 d), chronic cigarette smoking reduced clearance in both rats and dogs.

Further perusal of the subject indicates that, in the long term, there are decreases in clearance rates and thus longer retention of and higher doses from radioactive particles. The acute effects seem to be dependent not only on the dose of the smoke but on other factors, since different responses are seen in different subjects, even in the same experiment.

The possible role of the ^{210}Po in tobacco smoke as the causative agent in producing lung cancer in smokers was reviewed in chapter 4 (section V C). The results have been disparate, probably partly because of differences in the amount of polonium in different samples of tobacco, partly differences in the host response. Martell has been the most verbal champion of radioactivity as the causative agent. He seems to be willing to discount the experiments with negative results. It is interesting to note that Little and his associates conclude that the results in toto tend to support the hypothesis that ^{210}Po or ^{210}Pb in cigarette smoke may be a significant factor in the initiation of lung cancer in humans. (They point out that the radioactivity could easily be removed from tobacco without affecting flavor. However, this suggestion seems not to have resulted in any action by either industry or government.)

On balance, we must conclude as we did in chapter 4 that the highest concentrations of radioactivity found in tobacco might well be sufficient to initiate cancer, even without co-factors, while the lowest concentrations would have to be considered unlikely causative agents in themselves. The problem will not go away since it requires definitive answers to fundamental questions. A recent resurrection of the discussion comes from a 1982 letter from a group at the University of Massachusetts Medical Center published in the *New England Journal of Medicine* (Winters and Di Franze 1982). These authors bring to bear the fact that alpha particle ranges are short and average dose to lung is not a proper expression for the significant dose. They suggest that "The ^{210}Po alpha activity of cigarette smoke may be a very effective carcinogen if a multiple mutation mechanism is involved" (p. 365). Thus, features of the hot particle proposition appear in the context of production of lung cancer from cigarette smoke. The validity can be neither confirmed nor denied until the mechanisms are more fully worked out. Someday they will be. Meanwhile we can expect controversy.

C. SNAP, ROVER, Kiwi, NERVA

At the opening of the first large symposium on inhalation problems with radioactive materials (the Hanford symposium on Inhaled Radioactive Particles and Gases), Dr. William Lotz from the Division of Biology and Medicine of the AEC delivered a "Statement on the Problem" (Lotz 1964). He described urgent practical problems that required attention from inhalation toxicologists and aerosol experts. He exhorted his listeners to consider experimental work with a bearing on the practical problems of (1) the thermal energy devices using radioisotopes for the generation of electricity in space and at remote locations (SNAP—Systems for Nuclear Auxiliary Power); (2) Nuclear rocket propulsion (ROVER); and (3) the experimental reactor (Kiwi)^(a) to be used for development of nuclear rocket engines (NERVA).^(b) Related to these was the idea of a

(a) Kiwi seems not to be an acronym but to refer to the real bird which cannot fly. How did those who coined the name know it would never fly?

(b) Nuclear Engine for Rocket Vehicle Application.

nuclear-powered airplane. These problems were, of course, "special" and in addition to those of more routine operations.

1. SNAP

This is the only program of those above that went through development and became operational. Today there are many thermoelectric generators on satellites now in orbit, on the moon, and in remote areas of the world that obtain their heat from the presence of large quantities of radioisotopes. The first such source contained ^{210}Po and was demonstrated personally by President Eisenhower by having it light a small electric bulb on his desk. Later ^{90}Sr was used, but the alpha emitters have the advantage of requiring less shielding. Lotz (1964) lists eighteen materials used or proposed for SNAP devices. However, the choices gradually narrowed down, and ^{238}Pu became and is the most common material used. There is no question but the very considerable increase in demand for ^{238}Pu resulting from this choice led to much of the experimental work with this isotope we have already reviewed.

There were two major safety concerns with these devices in the minds of the biologists: mishaps during the early phases of launch, which would bring the device violently back to earth; and uncontrolled orbital decay and atmospheric re-entry. The engineers took care of the first problem by exceedingly sturdy construction, which withstood the most severe tests without breaching the source container. By contrast, it was determined that controlled re-entry from orbit could not be guaranteed and that the design should assure complete burn-up of the fuel core in the upper atmosphere. This decision was not satisfactory to the biologists.

These decisions were not reached overnight. There was a SNAP Hazards Safety Committee of the AEC, which weighed the alternatives diligently. Health hazards played an important role. Many meetings were held under the aegis of the Division of Biology and Medicine (DBM). The results of two of these were kindly made available to me by Dr. H. D. Bruner, who had much of the responsibility at Headquarters.^(a) The members were, in addition to Dr. Bruner, Roy Albert (NYU), William Bair (Hanford), Birney Fish (ORNL), Wright Langham (Los Alamos), Thomas Mercer (Rochester), Roger McClellan (Lovelace), Arthur Tamplin (Livermore), and William Lotz (DBM/USAEC). It was soon decided that gastrointestinal absorption was very low, and the protection of the cornified epidermal layers in the skin was sufficient to eliminate surface deposition and ingestion as important health problems. Inhalation and effects on lung were considered the major concern, although thought was given to gonads to the extent of careful calculations of how much the maximum possible amount from SNAP devices might add to the plutonium already accumulated from weapons testing fallout. It was considered not sufficient to make much difference biologically.

Obviously, particle size was an important parameter in estimating the inhalation hazard from a re-entry burn-up of a SNAP device. Many of the ideas that later triggered the hot particle issue came up for full discussion at the committee's meetings. It was agreed that full burn-up could probably result in a predominance of very small particles (i.e., it would be a fume). Thus, hot particles

(a) He is now at Bonita Springs, Florida. Dr. Bruner's reminiscences on a taped interview were also extremely helpful (Bruner 1979).

would not be present initially but might form later, either by coalescence in the atmosphere or in the lung. There was also consideration of the size of the populations potentially exposed and of what guidance should be given to agencies concerned in the event of a mishap.

An opportunity to test the calculations came unexpectedly. On April 21, 1964, a navigational satellite carrying a SNAP Device (SNAP 9-A) containing 17 kilocuries of ^{238}Pu (about 1 kg) failed to reach full orbital flight. The payload reentered the atmosphere in the Southern Hemisphere and burned completely. Long-term balloon and aircraft sampling and integrated fallout figures determined from samples of soil collected at sixty sites worldwide are discussed in detail by Hardy, Krey, and Volchok (1972). About 13 kilocuries could be accounted for, most of it in very small particle sizes, which remained aloft for years (residence half-time, fourteen months). The distribution, while localized in the Southern Hemisphere to begin with, gradually became worldwide, although it never became uniform. Because of the enormous dilution, no inhalation or other health hazards could be identified. Nevertheless, we must remember that none of the larger particles could have still been aloft by the time the sampling program got under way. We must assume that either there were very few or none of these, or that they fell in areas where they would not be detected (which was nearly everywhere in the area involved in the abort).

The health hazards associated with SNAP devices were probably as thoroughly discussed as any nuclear energy undertaking in proportion to their importance. So far, it appears that the planning and performance have been adequate. Even the one abort seems to have added only to the inventory of plutonium, not to discernible health effects.

2. ROVER, Kiwi, and NERVA

The possibility of developing nuclear-propelled rockets was a joint project of the AEC and the National Aeronautics and Space Administration. The Los Alamos Laboratory took a key role in developing the reactor technology and its adaptation to rocket engines. There was a prototype built for static testing in a remote area of the Nevada Test Site. There was also the idea that a modified reactor could propel an airplane if an airframe could be found that would separate the reactor and the crew by a suitable distance and still be airworthy. Neither device ever flew; the rocket primarily because of potential contamination problems, the airplane for the same reason, plus engineering problems.

There was an AEC Aerospace Nuclear Safety Committee with the same responsibilities (and I presume similar membership) as the SNAP Hazards Committee. The fuel elements of the experimental reactor contained about 10^{12} particles of ^{235}U carbide ($^{235}\text{UC}_2$) of about 100 to 200 μm in diameter (Dean and Langham 1969). Evidently it was expected that the rocket exhaust might contain some of these particles, but the chief concern was re-entry or failure to obtain orbit. It was very difficult to design a reactor core that could both produce a suitable thrust (e.g., by heating hydrogen) and be proof against rupture on impact. Certification that it would remain intact in an abort was not forthcoming. The particles would have undergone as many as 10^{13} fissions and have dose rates of 10^8 rad/hr at thirty minutes after reactor shutdown. These would indeed be hot particles!

The safety analysis in this case concerned both the hazard to skin, should even one such particle deposit on it, and the usual inhalation hazards. Their large size mitigated against their inhalation unless they broke up. Nevertheless,

some of Sanders's work at Hanford, already cited, left open the possibility of deposit of such particles in the upper respiratory tract. These workers urged experimental work by intratracheal instillation or surgical implantation to check on the effects produced by particles in the 100- to 300- μm range.

This author remembers meetings at which it was insisted that any nuclear rocket would have to blast off to at least orbital distance with chemical propellants. The nuclear power thrust, while lower, could last longer and get a payload on its way to interplanetary space if desired, but it could not be used in the earth's atmosphere. It has not been possible to find documentary proof, but it is this author's impression that the potential health hazards, both to skin and by inhalation, tipped the scales toward abandoning the project.

D. Organizational Considerations

Obviously, an effort as large as the work on inhalation of radioactive substances did not happen spontaneously. The bulk of the financing in the United States came through the AEC and its successors, the ERDA, DOE, and also the U.S. Air Force. The Department of Health, Education and Welfare was the second most active sponsor, particularly around problems of uranium miners and uranium mill tailings. Toward the end of the period of our interest, the EPA took over some functions and their financing, but not very much laboratory research. The Headquarters staff and AEC had major responsibilities for translating operational problems into research projects that would both attack the immediate problem and contribute to the ongoing acquisition of useful and meaningful knowledge. They were constantly evaluating progress, defending the need for and allocating funds, and promoting and coordinating the efforts of the several groups. Their role was a significant one to both the research and to the protection of the continuity of the effort, especially in long-term experiments.

An early planning session of significance and a good example of the role of the Headquarters Staff is seen in a 1961 meeting on the subject, "What Constitutes Respirable Dust?" The meeting was held at Los Alamos in January 1961. There were three university scientists, six participants from AEC contractor laboratories, three people from license compliance offices in the field, and six from various divisions at Headquarters. Two of the Headquarters staff were from Licensing and Regulation, two from Health and Safety, and one each from the Office of the General Counsel, and the Division of Compliance. The deliberations were made available to me by Dr. Donald M. Ross (Ross 1962, 1980), for many years Chief of the Health Protection Branch and a competent industrial hygienist.

With careful review of the literature, a decision was made to consider 10 μm the nominal upper limit for respirable dust if deposition in the nonciliated portion of the lung is implied. The concepts of respirable dust and selective sampling^(a), along the lines published later by Morrow (1964), and the decision to develop size-selective sampling devices were highlighted by this meeting. Furthermore, the fact that by "size" is meant an aerodynamic diameter with properties equivalent to a unit density sphere was emphasized. For many of the substances of interest to the AEC, this makes considerable difference. Table 9.20 illustrates this point vividly.

(a) As applied to insoluble particles.

TABLE 9.20. Equivalent Particle Diameters for Various Densities Compared with Unit Density

Material Density	H ₂ O 1.0	SiO ₂ 2.6	Yellow Cake 5.4	U ₃ O ₈ 8.4	UO ₂ 10.9
Diameter (in μ)	0.5	0.31	0.22	0.17	0.15
	1.0	0.62	0.43	0.35	0.31
	2.0	1.24	0.86	0.69	0.62
	3.0	1.86	1.29	1.03	0.92
	4.0	2.48	1.72	1.38	1.23
	5.0	3.10	2.15	1.73	1.54
	7.0	4.34	3.01	2.42	2.16
	10.0	6.20	4.30	3.45	3.08

Source: Reset from Hyatt 1960.

Even though taken from the accumulation of wisdom among the participants and from previously published work, it seems likely that a meeting and report of this type helped much to bring important concepts out of the confines of specialized areas.^(a)

Another useful type of coordination, which went above and beyond the budget submission and approval process, is exemplified in the Inhalation Toxicology Working Group managed largely by W. E. Lotz at Headquarters with encouragement and help from H. D. Bruner. We have already glimpsed the value of its operation in bringing people from the cognizant laboratories together for reviews of specific programs.

The general review of plutonium work nationwide in the early and mid-1970s by a series of Task Forces responsive to a Plutonium Committee of AEC was discussed in chapter 8. Much of the material in this review concerned inhalation studies. Likewise, a considerable portion of the 1977 Actinide Workshop at Seattle, described in chapter 8, concerned inhalation experiments under way and their responsiveness to the needs of the time.

When the AEC was about to be transmuted to ERDA, there was a thorough review of not only all work under way in the radioactive inhalation field, but postulates for new work in the inhalation toxicology of all forms of energy generation. An excerpt from the in-house document reviewing the problems and plans is given below.

The declaration by Congress on October 8, 1974 . . . to accelerate . . . development of all energy sources to meet the needs of present and future generations, and to make the nation self-sufficient in energy, also directed that public health and safety be concomitantly assured. The generation of new toxic aerosols by rapidly developing energy sources, superposed upon those agents presently responsible for an alarming increase in lung cancer in the general population and severely increased

(a) Remember that the numerous helpful reviews we have mentioned were not published yet.

chronic respiratory disease in industry, could rapidly magnify the danger of widespread disease caused by inhaled airborne contaminants. This will occur unless a comprehensive program is promptly implemented to define the nature, properties, environmental levels, and biological disposition of these airborne toxicants, as well as mechanisms of pulmonary or systemic disease caused by aerosolization of energy-related materials. Such a program must incorporate 1) identification of inhalation hazards and characterization of their sources, 2) studies of physical-chemical characteristics of air-borne particulates and gases that affect their physical and biological behavior, 3) evaluation of factors and processes that affect respiratory tract deposition and retention, 4) increased understanding of mechanisms, pathways, and kinetics of biological disposition of deposited agents, including cell-mediated and dissolutive clearance, translocation rates and fractions, and processes of elimination or detoxification, 5) identification of the nature and degree of deleterious effects, both acute and delayed, resulting from inhalation of toxic materials arising from, or related to nascent energy technologies, 6) establishment of primary and sequential dose-effect relationships, 7) identification of sensitive populations and studies of the influence of age or compounding diseases upon effects, 8) predictive models based upon experimental work, 9) evaluation of effects of localized concentrations vs. diffuse distributions of inhaled contaminants in critical tissues, 10) mechanisms of repair and recovery. (ERDA 1975)

This was followed by a detailed consideration of priorities for research in each of the named areas.

What broader or more comprehensive template could we need to judge our plans and the progress of our research in this field? What better way to conclude this chapter but to suggest that our progress and the unanswered questions remaining be reviewed against this template? If we as a nation fail to achieve our comprehensive research goals in inhalation toxicology, it cannot be attributed to inadequate planning at the scientific level in government, which continues to be the most likely single source of support for this important work.

VI. Summary and Commentary

As in most industrial environments, the primary route of entry of radioactive materials into the body was expected to be by inhalation of vapors, dusts, particles, or gases. This chapter considers the enormous efforts expended on inhalation of dust and particles. Chapter 10 considers radioactive gases and vapors.

There was a considerable effort during the years of World War II devoted to inhalation problems. There was an industrial hygiene air sampling program, both personal and area monitoring, and large experimental programs with animals to determine the behavior and effects of inhaled radioactive materials. The largest from the standpoint of both industrial measurements and experimental work concerned natural uranium. The bulk of these experiments on inhalation toxicology of uranium took place at the University of Rochester, and their discussion occupies considerable space in the chapter. Important adjuncts to this work included the development of aerosol science, particularly the role of particle size and the characterization of inhaled dusts. Since natural uranium is weakly radioactive, exposure methodologies did not need to be markedly different from those used for investigation of nonradioactive dusts.

Work at Berkeley and Chicago during World War II delved more into the inhalation of aerosols of more highly radioactive materials. In addition to rather crude burning wire procedures, several inhalation experiments were carried out using the off-gases from the Clinton "Pile," under the auspices of both Berkeley

and Chicago. There was, in addition, a small program at Rochester in which ^{210}Po aerosols were produced by volatilization from a heated wire and inhaled by rats.

In addition to enhancing greatly our knowledge of the role of particle size, these early experiments demonstrated that insoluble complexes of the inhaled radioactive materials were frequently formed and remained in the lung. This could occur even when the initial form was expected to be "soluble."

In the decades of the 1950s–1980s, the entire field of inhalation studies expanded greatly. Chicago and Berkeley cleaned up some tag ends from the war years. Rochester continued as a center for inhalation studies by developing special facilities, carrying forward the eleven-year study of uranium described in chapter 2, and by including this field in its extensive educational program. Indeed, it produced many of the individuals who went on to develop or take key roles in other inhalation programs.

Hanford began in the field in early 1950 using intratracheal instillation and was the first to demonstrate the production of a lung tumor by plutonium. Under the direction of W. J. Bair, Hanford (now Battelle, Pacific Northwest Laboratories) has become a major center for all aspects of the inhalation toxicology of radioactive materials. While primary emphasis was on plutonium and the actinides and on radon problems (as we saw in chapter 3), many other groups of radionuclides were investigated. The rather remarkable ability of plutonium to produce lung cancer forced experiments to lower and lower levels of exposure. Naturally, one does not produce dangerous aerosols of highly radioactive materials without special facilities and equipment. The Hanford program produced many original designs. Some of these are depicted in the chapter. They were noted for ability to add adjuvants, such as cigarette smoke, mine air dust, etc.

In the 1960s, a new center was built near Albuquerque, New Mexico, to attack the problem of inhaled fission products. This was managed by the Lovelace Foundation, originally directed by Randolph Lovelace and C. S. White. It later became the Inhalation Toxicology Research Institute and is under the direction of R. O. McClellan. Since many of the fission products are beta or beta-gamma emitters and thus produce more penetrating radiations than the alpha emitters emphasized at Rochester, and, in part, at Battelle, still more refinements of methodology were needed. The development of the facility is described in chapter 8, but the results appear in this chapter. The ITRI group did much of their work with an insoluble carrier aerosol as a vector in order to separate out contrasts in effects due to differences in radionuclides from those due to differences in aerosols. They also developed a reproducible monodisperse aerosol.

The group at New York University carried forward on a broad front. They had much connection with the analyses of industrial exposures, partly themselves and partly by collaboration with the AEC office of Health and Safety that was directed for many years by Merrill Eisenbud, who later spearheaded the radioactivity work at NYU.

There was also activity concerning inhalation of radioactive aerosols at Harvard (Little et al.), Pittsburgh (Cember), Cincinnati (Cember), Wayne State University (Vorwald), and the Naval Radiological Defense Laboratory (Cohn), and others.

In the early 1970s, the inhalation field was shaken by the "hot particle problem." This resulted from allegations by the Natural Resources Defense Council of Washington, D.C. that discrete, highly radioactive particles, either inhaled or formed in the lung, were much more likely to produce lung cancer than the

same radiation dose spread over a larger area. Nearly every laboratory diverted some of its attention to investigating these allegations. It was probably Los Alamos that was drawn in in the most *de novo* fashion. At Los Alamos, an extensive program was developed with microspheres (Richmond et al.). These uniformly-sized plastic spheres could be coated with various amounts of radio-nuclides (e.g., plutonium), injected, and, because their size was just right, lodged in the capillaries of the lung. They thus acted as a realistic surrogate for a "hot particle." In addition to the flurry of experimental work, several expert committees were convened on both sides of the Atlantic to address the problem. The results to date have confirmed the conclusions that could be drawn by sophisticated intuition, viz., that there is greater cell killing around the "hot particle" and that, in terms of carcinogenic potential, a diffuse source may be just as, if not more, dangerous in causing cancerous changes in cells.

There were also inhalation programs around special nuclear devices and the possibility of a one-point detonation of a nuclear device. These are described briefly in the chapter, but the results are reserved for chapter 14.

It is commonly stated that the enormous effort surrounding problems of the inhalation of radioactive materials led the way over the last decades for all of inhalation toxicology. This is true and surprising in view of the fact that technically the problems were difficult indeed. We must be thankful for the relative generosity and especially the steadfast reliability of the sponsoring agencies that allowed the work to progress logically. It is ill-suited to a small academic enterprise. The results have demonstrated that there can be no substitute for an actual inhalation experiment in approaching either a practical understanding of the behavior and effects of specific substances or the underlying physiology, pharmacology, and pathology of the respiratory system.

References

- Abrams, R., A. M. Potts, C. E. Beilman, I. Wender, W. Lohr, S. Postel, and L. L. Forker. 1946a. *Production and analysis of radioactive aerosols*, AEC report MDDC-795, completed July 1946, declassified March 1947.
- Abrams, R., H. C. Seibert, L. Forker, D. Greenberg, H. Lisco, L. Jacobson, and E. Simmons. 1946b. *Acute toxicity of intubated plutonium*. Metallurgical Laboratory report CH-3875, June 1946, declassified December 1955.
- Abrams, R., H. C. Seibert, A. M. Potts, L. L. Forker, D. Greenberg, S. Postel, and W. Lohr. 1946c. *Metabolism and distribution of inhaled plutonium in rats*. Metallurgical Laboratory report CH-3655, AEC report MDDC-677, October 1946, declassified February 1947.
- Abrams, R., H. C. Seibert, A. M. Potts, W. Lohr, and S. Postel. 1946d. *Metabolism of inhaled fission product aerosols*. Metallurgical Laboratory report CH-3485, AEC report MDDC-248, May 1946, declassified August 1966.
- Albert, R. E. and L. C. Arnett. 1955. Clearance of radioactive dust from the human lung. *AMA Arch. of Ind. Health* 12:99-106.
- Albert, R. E. and M. Lippmann. 1968. Pulmonary deposition and clearance of dust in man and animals. In *Fifth annual progress report*, pp. 87-93. New York: New York Univ. Institute of Environmental Medicine.
- Albert, R. E., M. Lippmann, J. Spiegelman, A. Liuzzi, and N. Nelson. 1967a. The deposition and clearance of radioactive particles in the human lung. *Arch. Environ. Health* 14:10-15.
- Albert, R. E., M. Lippmann, J. Spiegelman, C. Strehlow, W. Briscoe, P. Wolfson, and N. Nelson. 1967b. The clearance of radioactive particles from the human lung. In *Inhaled particles and vapours. II.*, ed. C. N. Davies, pp. 361-78. Proceedings of an international symposium held in Cambridge, England, September 28-October 1, 1965. Oxford-London-New York: Pergamon Press.

- Albert, R. E., H. T. Peterson, D. E. Bohning, and M. Lippmann. 1975. Short-term effects of cigarette smoking on bronchial clearance in humans. *Arch. Environ. Health* 30:361-67.
- Altshuler, B. 1958. Dosimetry from a Ru^{106} -coated platinum pellet. *Radiat. Res.* 9:626-32.
- Andersen, B. V. 1964. Plutonium aerosol particle size distributions in room air. *Health Phys.* 10:899-907.
- Anderson, E. C. and J. D. Perrings. 1978. Production and properties of radioactive microspheres for localized irradiation of lung tissue. *Health Phys.* 34:225-36.
- Anderson, E. C., L. M. Holland, J. R. Prine, and C. R. Richmond. 1974. Lung irradiation with static plutonium microspheres. In *Experimental lung cancer: Carcinogenesis and bioassays*, eds. E. Karbe and J. F. Park, pp. 430-42. Proceedings of a symposium held in Seattle, Wash., June 23-26, 1974. New York: Springer-Verlag.
- Anderson, E. C., L. M. Holland, J. R. Prine, D. M. Smith, and R. G. Thomas. 1978. Current summary of intravenous microsphere experiments. In *Biomedical and environmental research program of the LASL Health Division*, LA-7254-PR, pp. 19-21. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Asling, C. W. and G. Thilo. 1951. Radioautography. In *Quarterly report for October, November, December 1951*, UCRL-1694, pp. 2-5. Berkeley, Calif.: Univ. of Calif. Radiation Laboratory.
- Asling, C. W. and G. Thilo. 1952. Radioautographic studies of the pulmonary deposition of plutonium aerosols. In *Quarterly report for January, February, March 1952*, UCRL-1826, pp. 34-47. Berkeley, Calif.: Univ. of Calif. Radiation Laboratory.
- Bair, W. J. 1958. Translocation and excretion of pulmonary deposited plutonium oxide. HW-56636. Richland, Wash.: Hanford Atomic Products Operation.
- Bair, W. J. 1960. Radioisotope toxicity: From pulmonary absorption. In *Radioisotopes in the biosphere*, eds. R. S. Caldecott and L. A. Snyder, pp. 431-48. Proceedings of a symposium held in Minneapolis, October 19-23, 1959. Minneapolis: Univ. of Minn., Center for Continuation Study.
- Bair, W. J. 1961. Deposition, retention, translocation and excretion of radioactive particles. In *Inhaled particles and vapors*, ed. C. N. Davies, pp. 192-208. Proceedings of an international symposium held in Oxford, March 29-April 1, 1960. London: Pergamon Press.
- Bair, W. J. 1967. Untitled report presented at SNAP-SNPO meeting in Washington, D.C., June 23, 1967.
- Bair, W. J. 1970. *Plutonium inhalation studies. (A series of lectures given in Japan in 1969 at the invitation of the Japanese Atomic Energy Commission.)* BNWL-1221. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Bair, W. J. 1974. *The biological effects of transuranium elements in experimental animals*. Hearings of the Environmental Protection Agency, vol. 1, EPA ORP/CDS-75-1, Washington, D.C.
- Bair, W. J. and J. V. Dilley. 1967. Pulmonary clearance of $^{59}Fe_2O_3$ and $^{51}Cr_2O_3$ in rats and dogs exposed to cigarette smoke. In *Inhaled particles and vapours. II.*, ed. C. N. Davies, pp. 251-71. Proceedings of an international symposium held in Cambridge, England, September 28-October 1, 1965. Oxford-London-New York: Pergamon Press.
- Bair, W. J. and J. F. Park. 1968. Comparative deposition of four types of plutonium dioxides inhaled by dogs. In *Proceedings of the 1st international congress of radiation protection* held in Rome, September 5-10, 1966. Oxford-New York: Pergamon Press.
- Bair, W. J., J. F. Park, and W. J. Clarke. 1966. *Long-term study of inhaled plutonium in dogs*. AFWL TR-65214. Kirtland Air Force Base, N. Mex.: Air Force Weapons Laboratory.
- Bair, W. J., C. R. Richmond, and B. W. Wachholz. 1974. *A radiobiological assessment of the spatial distribution of radiation dose from inhaled plutonium*. WASH-1320. Washington, D.C.: U.S. Atomic Energy Commission.
- Bair, W. J., E. G. Tombropoulos, and J. F. Park. 1962. Distribution and removal of transuranic elements and cerium deposited by the inhalation route. In *Diagnosis and treatment of radioactive poisoning*, pp. 319-44. Proceedings of a symposium held in Vienna, October 15-18, 1962. Vienna: International Atomic Energy Agency.
- Bair, W. J. and D. H. Willard. 1961. *Plutonium inhalation studies. III. Effect of particle size and total dose on retention and translocation*. HW-68645. Richland, Wash.: Hanford Atomic Products.
- Bair, W. J., J. E. Ballou, J. F. Park, and C. L. Sanders. 1973. Plutonium in soft tissues with emphasis on the respiratory tract. Chapter 11 in *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh, pp. 503-68. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.

- Bair, W. J., B. C. Stuart, J. F. Park, and W. J. Clarke. 1964. Factors affecting retention, translocation and excretion of radioactive particles. In *Radiological health and safety in mining and milling of nuclear materials*, vol. 1, pp. 253-74. Proceedings of an symposium held in Vienna, August 26-31, 1963. Vienna: International Atomic Energy Agency.
- Bair, W. J., L. A. Temple, D. H. Willard, S. Marks, and D. G. Smith. 1958. Hazards of inhaled radioactive particles. In *Proceedings of the 1st international conference of radiation research*, held in Burlington, Vt., August 10-16, 1958.
- Ballou, J. E. 1974. Disposition of inhaled and intratracheally instilled ^{253}Es in rats. In *Pacific Northwest Laboratory annual report for 1973 to the USAEC Division of Biomedical and Environmental Research. Part 1 Biological sciences*. BNWL-1850, pt. 1, pp. 68-69. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Ballou, J. E., R. H. Busch, and G. E. Dagle. 1974. Histopathologic effect of intratracheally instilled $^{253}\text{EsCl}_3$ in rats. In *Pacific Northwest Laboratory annual report for 1973 to the USAEC Division of Biomedical and Environmental Research. Part 1 Biological sciences*. BNWL-1850, pt. 1, pp. 70-73. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Ballou, J. E., R. A. Gies, and A. H. Beasley. 1980. Comparative toxicology of inhaled actinide nitrates in rats. In *Pacific Northwest Laboratory annual report for 1979 to the DOE Assistant Secretary for Environment. Part 1 Biomedical sciences*. PNL-3300, Pt. 1, pp. 169-74. Richland, Wash.: Pacific Northwest Laboratory.
- Ballou, J. E., R. A. Gies, and A. C. Case. 1980. Disposition and late effects of inhaled $^{232}\text{UO}_2(\text{NO}_3)_2$ and $^{233}\text{UO}_2(\text{NO}_3)_2$ in rats. In *Pacific Northwest Laboratory annual report to the DOE Assistant Secretary for Environment. Part 1 Biomedical sciences. Pt. 1*, pp. 166-68. Richland, Wash.: Pacific Northwest Laboratory.
- Ballou, J. E., L. G. Smith, G. E. Dagle, and R. A. Gies. 1979. Late effects of inhaled $^{253}\text{Es}(\text{NO}_3)_3$ in the rat. In *Pacific Northwest Laboratory annual report for 1978 to the DOE Assistant Secretary for Environment. Part 1 Biomedical sciences*. PNL-2850, Pt. 1, pp. 3.30-3.32. Richland, Wash.: Pacific Northwest Laboratory.
- Baumberger, J. P. 1923. Amount of smoke produced from tobacco and its absorption in smoking as determined by electrical precipitation. *J. Pharmacol. Exp. Ther.* 21:47-57.
- Beiter, H., F. R. Gibb, and P. E. Morrow. 1975. Intramuscular retention of UO_3 and UO_2 . *Health Phys.* 29:273-77.
- Berke, H. L. and D. Deitch. 1970. Pathological effects in the rat after repetitive exposure to $^{152-154}\text{europium}$. In *Inhalation carcinogenesis*, eds. M. G. Hanna, Jr., P. Nettesheim, and J. R. Gilbert, CONF-691001, pp. 429-32. Proceedings of a conference held in Gatlinburg, Tenn., October 8-11, 1969. Springfield, Va.: National Technical Information Service.
- Berke, H. L. and A. C. DiPasqua. 1957. The distribution and excretion of polonium-210 after inhalation. UR-495. Rochester, N. Y.: Univ. of Rochester Atomic Energy Project.
- Berke, H. L. and A. C. DiPasqua. 1960. The accumulation of Po^{210} in the rat during multiple inhalant exposures. UR-573. Rochester, N. Y.: Univ. of Rochester Atomic Energy Project.
- Berke, H. L. and A. C. DiPasqua. 1964. Distribution and excretion of polonium-210. VIII: After inhalation by the rat. *Radiat. Res. Suppl.* 5:133-47.
- Berke, H. L. and L. M. Roslinski. 1971. The roentgenographic determination of tracheal mucociliary transport rate in the rat. *Am. Ind. Hyg. Assoc. J.* 32:174-78.
- Berke, H. L., G. H. Wilson, and E. S. Berke. 1968. Changes in size distribution of blood lymphocytes following inhalation of radio-europium. *Int. J. Radiat. Biol. & Relat. Stud. Phys. Chem. & Med.* 14:561-65.
- Bianco, A., F. R. Gibb, R. W. Kilpper, S. Landman, and P. E. Morrow. 1974. Studies of tantalum dust in the lungs. *Radiology* 112:549-56.
- Biophysical Society. 1974. Statement of science and technology advice and information service committee on *The hot particle problem*. Memorandum from Peter H. von-Hippel, ed., Univ. of Oregon.
- Bloom, W. 1948. *Histopathology of irradiation from external and internal sources*. National Nuclear Energy Series, div. IV, vol. 221, 1st ed. New York: McGraw-Hill.
- Boecker, B. B. 1962. Thorium inhalation studies. UR-605. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Boecker, B. B., F. L. Aguilar, and T. T. Mercer. 1964. A canine inhalation exposure apparatus utilizing a whole body plethysmograph. *Health Phys.* 10:1077-89.

- Boeckér, B. B., R. G. Thomas, and R. O. McClellan. 1975. Accumulation and retention of ^{137}Cs -labeled fused aluminosilicate particles by beagle dogs after repeated inhalation exposures. In *Inhaled particles IV*, ed. W. H. Walton, pt. 1(a), pp. 221-36. New York-Oxford: Pergamon Press.
- Boecker, B. B., F. F. Hahn, B. A. Muggenberg, R. O. McClellan, J. L. Mauderly and J. A. Pickrell. 1979a. Biological effects of repeated inhalation exposure of beagle dogs to relatively insoluble aerosols of ^{144}Ce , VI. In *Inhalation Toxicology Research Institute annual report 1978-1979*, LF-69, pp. 182-86. Albuquerque, N. Mex.: Lovelace Biomedical and Environmental Research Foundation.
- Boecker, B. B., B. S. Merickel, F. F. Hahn, J. L. Mauderly, and R. O. McClellan. 1979b. Toxicity of ^{144}Ce inhaled in a relatively insoluble form by immature beagle dogs. VIII. In *Inhalation Toxicology Research Institute annual report 1978-1979*, LF-69, pp. 92-95. Albuquerque, N. Mex.: Lovelace Biomedical and Environmental Research Foundation.
- Briant, J. K. and M. D. Allen. 1981. Techniques for generation of LMFBR-sodium aerosols. In *Pacific Northwest Laboratory annual report for 1980 to the DOE Assistant Secretary for Environment. Part 1: Biomedical sciences*. PNL-3700, pt. 1, pp. 112-13. Richland, Wash.: Pacific Northwest Laboratory.
- Brown, J. H., K. M. Cook, F. G. Ney, and T. Hatch. 1950. Influence of particle size upon the retention of particulate matter in the human lung. *Am. J. Public Health* 40:450-58. [Note: The term "retention" as used in this paper would now be "deposition."]
- Bruner, H. D. 1967. Pulmonary radiotoxicology. In *Proceedings of the biological sciences symposium held September 29, 1967*. SC-M-67-2973. Albuquerque, N. Mex.: Sandia Laboratories.
- Bruner, H. D. 1979. Personal interview at Delray Beach, Fla., November 1979.
- Burchsted, C. A. 1981. An index to the 1st through the 16th AEC/ERDA/DOE Nuclear Air Cleaning Conference. DOE/TIC-11405. Washington, D.C.: U.S. Department of Energy.
- Cadle, R. D. 1965. *Particle size: Theory and industrial applications*. New York: Reinhold Publishing Corp.
- Cannon, W. C., E. F. Blanton, and K. E. McDonald. 1983. The flow-past chamber: An improved nose-only exposure system for rodents. *Am. Ind. Hyg. Assoc. J.* 44:923-28.
- Cannon, W. C. (principal investigator), E. F. Blanton, J. K. Briant, J. R. Decker, A. L. Moen, O. R. Moss, E. J. Rossignol, D. L. Stevens, and D. H. Willard. 1982. Aerosol technology development. In *Pacific Northwest Laboratory annual report for 1981 to the DOE Office of Energy Research. Part 1: Biomedical sciences*. PNL-4100, pt. 1, pp. 55-59. Richland, Wash.: Pacific Northwest Laboratory.
- Casarett, L. J. 1956. *Autoradiographic study of the effects of route of administration on distribution of polonium-210*. UR-447. Rochester, N. Y.: Univ. of Rochester Atomic Energy Project. Also *Radiat. Res. Suppl.* 5:93-105.
- Casarett, L. J. 1960. Some physical and physiological factors controlling the fate of inhaled substances: II. Retention. *Health Phys.* 2:379-86.
- Casarett, L. J. 1964a. Distribution and excretion of polonium-210. IX. Deposition, retention, and fate after inhalation by "nose-only" exposure, with notes on mechanics of deposition and clearance and comparison of routes of administration. *Radiat. Res. Suppl.* 5:148-65.
- Casarett, L. J. 1964b. XII. Autoradiographic observations after inhalation of polonium-210 in rats. *Radiat. Res. Suppl.* 5:187-204.
- Casarett, L. J. and B. Epstein. 1966. Deposition and fate of inhaled iron-59 oxide in rats. *Am. Ind. Hyg. Assoc. J.* 27:533-38.
- Casarett, L. J. and P. S. Milley. 1964. Alveolar reactivity following inhalation of particles. *Health Phys.* 10:1003-11.
- Casarett, L. J. and P. E. Morrow. 1964. Distribution and excretion of polonium-210. XI. Autoradiographic studies after intratracheal administration in the rabbit. *Radiat. Res. Suppl.* 5:175-86.
- Casarett, L. J., S. Bless, R. Katz, and J. K. Scott. 1960. Retention and fate of iridium-192 in rats following inhalation. *Am. Ind. Hyg. Assoc. J.* 21:414-18.
- Cember, H. 1964a. Empirical establishment of cancer—Associated dose to the lung from ^{144}Ce . *Health Phys.* 10:1177-80.
- Cember, H. 1964b. Pulmonary cancer from deposited radioactive materials in the lung. In *Biological health and safety in mining and milling of nuclear materials*, vol. 1, pp. 307-15. Proceedings of a symposium held in Vienna, August 26-31, 1963. Vienna: International Atomic Energy Agency.

- Cember, H. and J. A. Watson. 1958a. Bronchogenic carcinoma from radioactive barium sulfate. *AMA Arch. Ind. Health* 17:230-35.
- Cember, H. and J. A. Watson. 1958b. Carcinogenic effects of strontium 90 beads implanted in the lungs of rats. *Am. Ind. Hyg. Assoc. J.* 19:36-42.
- Cember, H., J. A. Watson, and T. B. Grucci. 1956. Pulmonary radiation effects as a function of absorbed energy distribution. *Am. Ind. Hyg. Assoc. Q.* 17:397-400.
- Cember, H., J. A. Watson, and T. B. Grucci. 1957. Pulmonary effects from radioactive thallium-activated clay particles. *AMA Arch. Ind. Health* 15:449-50.
- Cember, H., T. F. Hatch, J. A. Watson, and T. B. Grucci. 1954. Pulmonary penetration of particles administered by intratracheal insufflation. *Arch. Ind. Hyg. Occup. Med.* 10:124-29.
- Cember, H., T. F. Hatch, J. A. Watson, and T. Grucci. 1955. Pulmonary effects from radioactive barium sulfate dust. *Arch. Ind. Health* 12:628-34.
- Clarkson, T. and A. Rothstein. 1964. The excretion of volatile mercury by rats injected with mercuric salts. *Health Phys.* 10:1115-21.
- Cohen, B. S., M. Eisenbud, and N. H. Harley. 1980. Measurement of the α -radioactivity on the mucosal surface of the human bronchial tree. *Health Phys.* 39:619-32.
- Cohn, S. H. 1959. *Hearings of the Joint Committee on Atomic Energy*, June 1959.
- Cohn, S. H., W. B. Lane, J. K. Gong, R. K. Fuller, and W. L. Milne. 1957a. *Studies on the metabolic and inhaled aerosols of strontium and lanthanum. II. The metabolism of an inhaled and ingested simulant of fallout produced by a land-based nuclear detonation.* USNRDL-TR-118. Washington, D.C.: U.S. Naval Radiological Defense Laboratory.
- Cohn, S. H., W. B. Lane, J. K. Gong, J. C. Sherwin, R. K. Fuller, L. L. Wiltshire, and W. L. Milne. 1955. *Uptake, distribution, and retention of fission products in tissues of mice exposed to a simulant of fallout from a nuclear detonation. I. Simulant of fallout from a detonation under seawater.* USNRDL-TR-77. Washington, D.C.: U.S. Naval Radiological Defense Laboratory.
- Cohn, S. H., W. B. Lane, J. K. Gong, J. C. Sherwin, and W. L. Milne. 1956. Inhalation and retention of simulated radioactive fall-out by mice. I. Study of a simulant of fall-out from nuclear detonation under sea water. *AMA Arch. Ind. Health* 14:333-40.
- Cohn, S. H., W. B. Lane, J. K. Gong, L. Weisbecker, and W. L. Milne. 1957b. *Studies on the metabolic and inhaled aerosols of strontium and lanthanum.* USNRDL-TR-175. Washington, D.C.: U.S. Naval Radiological Defense Laboratory.
- Cohn, W. E. 1948. Toxicity of inhaled or ingested radioactive products. *Nucleonics* 3(1):21-26.
- Cohn, W. E. 1980. Toxicity of inhaled or ingested radioactive products. Reprinted as a landmark paper with comments by J. N. Stannard in *Health Phys.* 38:1016-20.
- Commission on Radiation Protection [Federal Republic of Germany]: 1978. On the toxicity of inhaled hot particles with special reference to plutonium. *Radiat. Environ. Biophys.* 15:1-11.
- Craig, D. K. 1962. *Interactions between radionuclides and aerosols in the respirable size range.* Paper presented at a nuclear reaction chemistry conference held in Gatlinburg, Tenn., October 1962.
- Craig, D. K., J. R. Decker, R. L. Buschbom, D. L. Catt, and J. F. Park. 1972. Relationships between respiration parameters of unanesthetized adult beagle dogs during training and during $^{239}\text{PuO}_2$ aerosol inhalation exposures. In *Pacific Northwest Laboratory annual report for 1971 to the USAEC Division of Biology and Medicine. Vol. 1 Life Sciences, Part 1 Biological sciences.* BNWL-1650, pt. 1, pp. 200-211. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Dagle, G. E., J. E. Lund, and J. F. Park. 1976. Pulmonary lesions induced by inhaled plutonium in beagles. In *The health effects of plutonium and radium*, ed. W. S. S. Jee, pp. 161-67. Salt Lake City: The J. W. Press.
- Dagle, G. E. (principal investigator), A. C. Case, J. F. McShane, J. G. Powers, H. A. Ragan, S. E. Rowe, R. E. Schirmer, D. L. Stevens, R. E. Weller, and E. L. Wierman. 1982. Inhaled plutonium nitrate in dogs. In *Pacific Northwest Laboratory annual report for 1981 to the DOE Office of Energy Research. Part 1 Biomedical sciences.* PNL-4100, pt. 1, pp. 73-76. Richland, Wash.: Pacific Northwest Laboratory.
- Dailey, M., I. Wender, and R. Abrams. 1945. *Tracer studies with inhaled 1.0 year ruthenium.* Metallurgical Laboratory report MDDC-420, declassified October 21, 1946.
- Dautrebande, L. 1962. *Microaerosols.* New York: Academic Press.
- Dean, P. N. and W. H. Langham. 1969. Tumorigenicity of small highly radioactive particles. *Health Phys.* 16:79-84.

- Dennis, R., ed. 1976. *Handbook on aerosols*. TID-26608. Springfield, Va.: National Technical Information Service. [Earlier edition in 1950 by U.S. Office of Scientific Research and Development of the National Defense Research Committee.]
- Dockum, N. L. and J. W. Healy. 1955. *Spot diameter method of quantitative autoradiography of Ru^{106} particles in lung tissue*. HW-36760. Richland, Wash.: Hanford Works.
- Dolphin, G. W. 1974. *Hot particles*. Radiological Protection Bulletin 8. Harwell, Didcot, Berkshire, England: National Radiological Protection Board.
- Drinker, P. and T. Hatch. 1954. *Industrial dust. Hygienic significance, measurement and control*, 2d ed. New York: McGraw-Hill.
- Drinker, P., R. M. Thomson, and J. L. Finn. 1928. Quantitative measurements of the inhalation, retention, and exhalation of dusts and fumes by man. I. Concentrations of 50 to 450 MG. per cubic meter. *J. Ind. Hyg. Toxicol.* 10:13-25.
- Eisenbud, M. 1952. Retention, distribution and elimination of inhaled particulates. *Arch. Ind. Hyg. Occup. Med.* 6:214-25.
- Eisenbud, M. 1973. *Environmental radioactivity*, 2d ed. New York-London: Academic Press.
- Eisenbud, M. and H. G. Petrow. 1964. Radioactivity in the atmospheric effluents of power plants that use fossil fuels. *Science* 144:288-89.
- Eisenbud, M. and J. A. Quigley. 1956. Industrial hygiene of uranium processing. *AMA Arch. Ind. Health* 14:12-22.
- ERDA. See Energy Research and Development Administration.
- Energy Research and Development Administration. 1975. Excerpt from planning document concerning inhalation problems associated with energy production. ERDA, Division of Biological and Environmental Research.
- Failla, G. 1942. *Tolerance concentrations of radioactive gases in air*. Metallurgical Laboratory report CH-1347, February 1944, declassified January 1953.
- Fairhall, L. T. and R. R. Sayers. 1940. *The relative toxicity of lead and some of its common compounds*. Bull. 253. Washington, D.C.: U.S. Public Health Service.
- Farlow, N. H. and W. R. Schell. 1957. *Physical, chemical and radiological properties of slurry particulate fallout collected during Operation Redwing*. USNRDL-TR-170. Washington, D.C.: U.S. Naval Radiological Defense Laboratory.
- Ferin, J. 1972. Observations concerning alveolar dust clearance. *Ann. N.Y. Acad. Sci.* 200:66-72.
- Ferin, J. and L. J. Leach. 1973. The effect of SO_2 on lung clearance of TiO_2 particles in rats. *Am. Ind. Hyg. Assoc. J.* 34:260-63.
- Filipy, R. E., J. L. Pappin, D. L. Stevens, and S. G. Irby. 1980. Effects of cigarette smoke exposure on pulmonary clearance of $^{239}PuO_2$ in rats. In *Pacific Northwest Laboratory annual report for 1979 to the DOE Assistant Secretary for Environment. Part 1 Biomedical sciences*. PNL-3300, Pt. 1, pp. 128-30. Richland, Wash.: Pacific Northwest Laboratory.
- Fink, R. 1950. *Biological studies with polonium, radium, and plutonium*. National Nuclear Energy Series, div. VI, vol. 3. New York: McGraw-Hill.
- Fish, B. R. 1961. Inhalation of uranium aerosols by mouse, rat, dog and man. In *Inhaled particles and vapours*, ed. C. N. Davies, pp. 151-66. Proceedings of an international symposium held in Oxford, March 29-April 1, 1960. London: Pergamon Press.
- Fisher, D. R., ed. 1983. *Current concepts in lung dosimetry*. CONF-820492-P1, PNL-SA-11049. Proceedings of a special workshop held in Salt Lake City, April 21-22, 1982. Oak Ridge, Tenn.: Technical Information Center.
- Friedell, H. (in press). *An overview of research in radiation biology and protective measures in the Manhattan Project during the war years, 1942-1946*.
- Friedlander, S. K. 1977. *Smoke, dust and haze: Fundamentals of aerosol behavior*. New York: John Wiley & Sons.
- Gallimore, J.-C., G. A. Boyd, and J. N. Stannard. 1954. An autoradiographic study of the distribution of polonium in the rat during 24 hours after intravenous injection. *Anat. Rec.* 118:253-74.
- Gates, O. and S. Warren. 1961. Histogenesis of lung carcinoma in mice induced by gamma radiation. *Arch. Pathol.* 71:693-713.
- Geesaman, D. P. 1968. *An analysis of the carcinogenic risk from an insoluble alpha-emitting aerosol deposited in deep respiratory tissue*. UCRL-50387 and UCRL-50387 Addendum. Livermore, Calif.: Lawrence Livermore Laboratory.
- Gibb, F. R. and P. E. Morrow. 1962. Alveolar clearance in dogs after inhalation of an iron 59 oxide aerosol. *J. Appl. Physiol.* 17:429-32.

- Goodrich, R. M. and R. G. Thomas. 1963. *Data procurement and processing for the fission product inhalation program using an automatic read out counting system*. LF-13. Albuquerque, N. Mex.: Lovelace Biomedical and Environmental Research Foundation, Fission Product Inhalation Laboratory.
- Green, H. L. and W. R. Lane. 1957. *Particulate clouds: Dusts, smokes and mists. Their physics and physical chemistry and industrial and environmental aspects*. Princeton: D. Van Nostrand.
- Hackett, P. L., A. J. Clary, D. D. Mahlum, J. K. Briant, D. L. Catt, and L. R. Peters. 1981a. Biological behavior of inhaled LMFBF-fuel-sodium aerosols in beagle dogs. In *Pacific Northwest Laboratory annual report for 1980 to the DOE Assistant Secretary for Environment. Part 1 Biomedical sciences*. PNL-3700, pt. 1, pp. 119-21. Richland, Wash.: Pacific Northwest Laboratory.
- Hackett, P. L., D. D. Mahlum, R. L. Music, and J. K. Briant. 1981b. Biological behavior of LMFBF-fuel-sodium aerosols in rodents. In *Pacific Northwest Laboratory annual report for 1980 to the DOE Assistant Secretary for Environment. Part 1 Biomedical sciences*. PNL-3700, pt. 1, pp. 116-18. Richland, Wash.: Pacific Northwest Laboratory.
- Hahn, F. F. and B. B. Boecker. 1980. Tumors of the tracheobronchial lymph nodes in beagle dogs after inhalation of a relatively insoluble form of cerium-144. In *Pulmonary toxicology of respirable particles*, eds. C. L. Sanders, F. T. Cross, G. E. Dagle, and J. A. Mahaffey, CONF-791002, pp. 591-600. Proceedings of the 19th annual Hanford life sciences symposium held in Richland, Wash., October 22-24, 1979. Springfield, Va.: National Technical Information Service.
- Hahn, F. F., D. L. Lundgren, and R. O. McClellan. 1980. Repeated inhalation exposure of mice to $^{144}\text{CeO}_2$. II. Biologic effects. *Radiat. Res.* 82:123-37.
- Hahn, F. F., R. O. McClellan, B. B. Boecker, C. H. Hobbs, R. K. Jones, D. L. Lundgren, J. L. Mauderly, B. S. Merickel, B. A. Muggenburg, J. A. Pickrell, H. C. Redman, B. R. Scott, and M. B. Snipes. 1979a. Toxicity studies of inhaled beta emitting nuclides—Status report. In *Inhalation Toxicology Research Institute annual report 1978-1979*. LF-69, pp. 51-56. Albuquerque, N. Mex.: Lovelace Biomedical and Environmental Research Foundation.
- Hahn, F. F., B. A. Muggenburg, B. B. Boecker, J. L. Mauderly, R. O. McClellan, and J. A. Pickrell. 1979b. Toxicity of ^{144}Ce inhaled in a relatively insoluble form by beagle dogs. XII. In *Inhalation Toxicology Research Institute annual report 1978-1979*. LF-69, pp. 83-91. Albuquerque, N. Mex.: Lovelace Biomedical and Environmental Research Foundation.
- Hahn, F. F., B. A. Muggenburg, B. B. Boecker, J. L. Mauderly, R. O. McClellan, and J. A. Pickrell. 1979c. Toxicity of ^{144}Ce inhaled in a relatively insoluble form by beagle dogs. VIII. In *Inhalation Toxicology Research Institute annual report 1978-1979*. LF-69, pp. 96-100. Albuquerque, N. Mex.: Lovelace Biomedical and Environmental Research Foundation.
- Hamilton, J. G. 1944. *Metabolism of fission products*. Metallurgical Laboratory report CH-1460, February 1944, declassified March 1952.
- Hamilton, J. G. 1945. *Tracer studies on fission product metabolism*. Metallurgical Laboratory report CH-2673, prepared February 1945, declassified June 1947.
- Hamilton, J. G. and K. G. Scott. 1944. *Emanation studies—Animal experiments*. Metallurgical Laboratory report CH-1460 (A-2050).
- Hardy, E. P., Jr., P. W. Krey, and H. L. Volchok. 1972. *Global inventory and distribution of Pu-238 from SNAP-9A*. HASL-250. New York: Health and Safety Laboratory.
- Harley, J. H. 1981. Personal communication accompanied by excerpts from a brochure describing the Health and Safety Laboratory and its work, and selected reprints.
- Hayes, A. D. and A. Rothstein. 1962. The metabolism of inhaled mercury vapour in the rat studied by isotope techniques. *J. Pharmacol. Exp. Ther.* 138:1-10.
- Healy, J. W., C. R. Richmond, and E. C. Anderson. 1974. *A review of the Natural Resources Defense Council petition concerning limits for insoluble alpha emitters*. LA-5810-MS. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Henle, R. C. and P. E. Branson. 1969. *Evaluation of internally deposited $^{241}\text{americium}$ from bioassay data*. BNWL-SA-2047. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Hewlett, R. G. and F. Duncan. 1969. Atomic shield, 1947/1952. In *History of the United States Atomic Energy Commission*, vol. II, chapter 10. Univ. Park-London: Pa. State Univ. Press.
- Hodge, J. C. 1980. Taped personal interview, October 25, 1980.

- Hursh, J. B. and T. T. Mercer. 1970. Measurement of ^{212}Pb loss rate from human lungs. *J. Appl. Physiol.* 28:268-74.
- Hyatt, E. C. 1960. A study of two-stage air samplers designed to simulate the upper and lower respiratory tract. LA-2400. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Hyatt, E. C., W. D. Moss, and H. F. Schulte. 1959. Particle size studies on uranium aerosols from machining and metallurgy operations. *Am. Ind. Hyg. Assoc. J.* 20:99-107.
- ICRP. See International Commission on Radiological Protection.
- International Commission on Radiological Protection. 1980. *Biological effects of inhaled radionuclides*. Publ. no. 31, Annals of the ICRP, vol. 4, no. 1/2. New York-Oxford: Pergamon Press.
- Johnson, R. F., Jr. and P. L. Ziemer. 1971. The deposition and retention of inhaled $^{152-154}\text{Eu}$ oxide in the rat. *Health Phys.* 20:187-93.
- Kanapilly, G. M., Q. G. Raabe, C. H. T. Goh, and R. A. Chimenti. 1973. Measurement of *in vitro* dissolution of aerosol particles for comparison to *in vivo* dissolution in the lower respiratory tract after inhalation. *Health Phys.* 24:497-507.
- Karagianes, M. T., J. L. Beamer, D. K. Craig, W. T. Kaune, J. R. Decker, and W. C. Cannon. 1976. $^{239}\text{PuO}_2$ aerosol exposure of miniature swine. In *Pacific Northwest Laboratory annual report for 1975 to the ERDA Division of Biomedical and Environmental Research. Part 1 Biomedical sciences*. BNWL-2000, pt. 1, pp 47-48. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Kastenbaum, M. A. and T. J. Mitchell. 1970. Studies in inhalation carcinogenesis: A critique. In *Inhalation carcinogenesis*, eds. M. G. Hanna, Jr., P. Nettesheim, and J. R. Gilbert, pp. 445-53. Proceedings of a conference held in Gatlinburg, Tenn.: October 8-11, 1969. Springfield, Va.: National Technical Information Service.
- Kennedy, A. R., J. Worcester, and J. B. Little. 1977. Deposition and localization of polonium-210 intratracheally instilled in hamster lung as determined by autoradiography of freeze-dried sections. *Radiat. Res.* 69:553-72.
- Kilpper, R. W., A. Bianco, F. R. Gibb, S. Landman, and P. E. Morrow. 1976. Uptake and retention of insufflated tantalum by lymph nodes. In *Radiation and the lymphatic system*, ed. J. E. Ballou, CONF-740930, pp. 46-53. Proceedings of the 14th annual Hanford biology symposium held in Richland, Wash., September 30-October 2, 1974. Springfield, Va.: National Technical Information Service.
- Kimball, C. and R. Fink. 1950. Inhalation of volatilized polonium by rats. In *Biological studies with polonium, radium, and plutonium*. National Nuclear Energy Series, div. VI, vol. 3, pp. 89-111. New York: McGraw-Hill.
- Kotrappa, P. 1968. Dose to respiratory tract from continuous inhalation of radioactive aerosol. UR-49-964. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Kotrappa, P. and O. R. Moss. 1971. Production of relatively monodisperse aerosols for inhalation experiments by aerosol centrifugation. *Health Phys.* 21:531-35.
- Kotrappa, P., C. J. Wilkinson, and H. A. Boyd. 1972. Technology for the production of monodisperse aerosols of oxides of transuranic elements for inhalation experiments. *Health Phys.* 22:837-43.
- Koval, G. 1945. *Determination of particulate air-borne long-lived activity*. AEC report MDDC-1503, June 1945, declassified December 1947.
- Kuschner, M., S. Laskin, N. Nelson, and B. Altschuler. 1958. Radiation induced bronchogenic carcinoma in rats. *Am. J. Pathol.* 34:554.
- Kuschner, M., N. Nelson, S. Laskin, J. Harley, and B. Altschuler. 1957. *Tissue reaction to intrapulmonary radiation*. Progress report on AEC Contract AT(301)-1925. New York: New York Univ., Institute of Industrial Medicine.
- LaBauve, R. J., A. L. Brooks, J. L. Mauderly, F. F. Hahn, H. C. Redman, C. Macken, D. O. Slauson, J. A. Mewhinney, and R. O. McClellan. 1980. Cytogenetic and other biological effects of $^{239}\text{PuO}_2$ inhaled by the rhesus monkey. *Radiat. Res.* 82:310-35.
- LaBelle, C. W. 1949. The relation of particle size to toxicity. In Voegtlin and Hodge 1949, pp. 505-12.
- LaBelle, C. W. 1953. Relation of mean particle size to toxicity of particulate uranium dioxide. In Voegtlin and Hodge 1953, pp. 1730-75.
- LaBelle, C. W., C. E. Booth, R. B. Barrett, and A. Rothstein. 1953. Deposition of uranium dioxide in rabbits. In Voegtlin and Hodge 1953, pp. 1678-1700.

- Lafuma, J. C.: 1978, 'Etude expérimentale de l'évaluation des taux d'induction des cancers pulmonaires avec différents radioéléments émetteurs inhalés: Influence de divers paramètres et comparaisons avec les données obtenues chez les mineurs d'uranium. In *Late biological effects of ionizing radiation*, STI/PUB/489, vol. 2. Proceedings of a symposium held in Vienna, March 13-17, 1978. Vienna: International Atomic Energy Agency.
- Lafuma, J., J. C. Nénot, M. Morin, R. Massé, H. Metivier, H. Nobilé, and W. Skupinski. 1974. Respiratory carcinogenesis in rats after inhalation of radioactive aerosols of actinides and lanthanides in various physicochemical forms. In *Experimental lung cancer: Carcinogenesis and bioassays*, eds. E. Karbe and J. F. Park, pp. 443-53. Proceedings of a symposium held in Seattle, Wash., June 23-26, 1974. New York: Springer-Verlag.
- Lanz, H. and J. Teresi. 1945. *The metabolism of short-lived air-borne fission products*. AEC report MDDC-954.
- Laskin, S., M. Kushner, B. Altshuler, and N. Nelson. 1964. Tissue reactions and dose relationships in rats following intrapulmonary beta radiation. *Health Phys.* 10:1229-33.
- Laskin, S., M. Kushner, N. Nelson, B. Altshuler, J. H. Harley, and M. Daniels. 1963. Carcinoma of the lung in rats exposed to the β -radiation of intrabronchial ruthenium¹⁰⁶ pellets. I. Dose-response relationships. *J. Natl. Cancer Inst.* 31:219-31.
- Lauterbach, K. E., A. D. Hayes, and M. A. Coelho. 1956. An improved aerosol generator. *AMA Arch. Ind. Health* 13:156-60.
- Lauterbach, K. E., R. H. Wilson, S. Laskin and D. W. Meir. 1952. *Design of an oscillating thermal precipitator*. UR-199. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Letavet, A. A. and E. B. Kuryandskaya. *The toxicology of radioactive substances*. [Several volumes on different radio-elements produced over the period 1962-1970. Translation sponsored by United Kingdom Atomic Energy Authority, Harwell-Didcot-Berks; edited by G. W. Dolphin and published by Pergamon Press, Oxford-London-New York. Original Russian version published by Medgiz, Moscow.]
- Lie, R. 1964. Deposition and retention of ¹³⁷Cs in the rat following inhalation of the chloride and the nitrate. *Health Phys.* 10:1071-76.
- Lie, R., R. C. Thomas, and J. K. Scott. 1960. The distribution and excretion of thallium-204 in the rat, with suggested MPC's and a bio-assay procedure. *Health Phys.* 2:334-40.
- Lippmann, M. 1970a. Deposition and clearance of inhaled particles in the human nose. *Ann. Otol. Rhinol. & Laryngol.* 79:519-28.
- Lippmann, M. 1970b. Experimental inhalation studies—Equipment and procedures. In *Inhalation carcinogenesis*, eds. M. G. Hanna, Jr. P. Nettesheim, and J. R. Gilbert, pp. 55-76. Proceedings of a conference held in Gatlinburg, Tenn., October 8-11, 1979, Springfield, Va.: National Technical Information Service.
- Lippmann, M. and R. E. Albert. 1969. The effect of particle size on the regional deposition of inhaled aerosols in the human respiratory tract. *Am. Ind. Hyg. Assoc. J.* 30:257-75.
- Lippmann, M. and W. B. Harris. 1962. Size-selective samplers for estimating 'respirable' dust concentrations. *Health Phys.* 8:155-63.
- Lisco, H. 1959. Autoradiographic and histopathologic studies in radiation carcinogenesis of the lung. *Lab. Invest.* 8:162-70.
- Lisco, H. and M. P. Finkel. 1949. Observations on lung pathology following the inhalation of radioactive cerium. *Fed. Proc.* 8:360-61.
- Little, J. B., B. N. Grossman, and W. F. O'Toole. 1970. Respiratory carcinogenesis in hamsters induced by polonium-210 alpha radiation and benzo(a)pyrene. In *Morphology of experimental respiratory carcinogenesis*, eds. P. Nettesheim, M. G. Hanna, Jr., and J. W. Deatherage, Jr., CONF-700501, pp. 383-94. Proceedings of a conference held in Gatlinburg, Tenn., May 13-16, 1970. Springfield, Va.: National Technical Information Service.
- Little, J. B., B. N. Grossman, and W. F. O'Toole. 1973. Factors influencing the induction of lung cancer in hamsters by intratracheal administration of ²¹⁰Po. In *Radionuclide carcinogenesis*, eds. C. L. Sanders, R. H. Busch, J. E. Ballou, and D. D. Mahlum, CONF-720505, pp. 119-37. Proceedings of the 12th annual Hanford biology symposium held in Richland, Wash., May 10-12, 1972. Springfield, Va.: National Technical Information Service.
- Little, J. B. and A. R. Kennedy. 1979. Evaluation of alpha radiation-induced respiratory carcinogenesis in Syrian hamsters: Total dose and dose-rate. *Prog. Exp. Tumor Res.* 24:356-69.
- Little, J. B., A. R. Kennedy, and R. B. McGandy. 1978. Effect of dose distribution on the induction of experimental lung cancer by alpha radiation. *Health Phys.* 35:595-606.

- Little, J. B., R. B. McGandy, and A. R. Kenriedy. 1978. Interactions between polonium-210 α -radiation, benzo(a)pyrene, and 0.9% NaCl solution instillations in the induction of experimental lung cancer. *Cancer Res.* 38:1929-35.
- Lotz, W. E. 1964. Symposium of inhaled radioactive particles and gases—Statement on the problem. *Health Phys.* 10:863-66.
- Mahaffey, J. A. and C. L. Sanders. 1979. Estimation of risk from lung cancer induced by inhaled alpha-emitting radionuclides at very low doses. In *Pacific Northwest Laboratory annual report for 1978 to the DOE Assistant Secretary for Environment. Part 1 Biomedical sciences.* PNL-2850, pt. 1, pp. 3.37-3.39. Richland, Wash.: Pacific Northwest Laboratory.
- Mahaffey, J. A., C. L. Sanders, J. F. Park, and G. E. Dagle. 1980. A comparison of metabolism and late effects in dogs and rats exposed to $^{239}\text{PuO}_2$. In *Pacific Northwest Laboratory annual report for 1979 to the DOE Assistant Secretary for Environment. Part 1 Biomedical sciences.* PNL-3300, pt. 1, pp. 126-27. Richland, Wash.: Pacific Northwest Laboratory.
- Marinelli, L. D. and P. F. Gustafson. 1952. Progress report: Rate of disappearance of RaSO_4 dust from the human lung. *Quarterly report.* ANL-4745, p. 47. Argonne, Ill.: Argonne National Laboratory.
- Marinelli, L. D., H. F. Lucas, P. F. Gustafson, and C. E. Miller. 1958. Excretion and retention of Ra^{226} in humans: A 2312-day follow-up of a single inhalation case. ANL-5967, pp. 54-57. Argonne, Ill.: Argonne National Laboratory.
- Marinelli, L. D., W. P. Norris, P. F. Gustafson, and T. W. Speckman. 1953. Transport of radium sulfate from the lung and its elimination from the human body following single accidental exposures. *Radiology* 61:903-15.
- May, K. R. 1945. The cascade impactor: An instrument for sampling coarse aerosols. *J. Sci. Instrum.* 22:187-95.
- Mayneord, W. V. and R. H. Clarke. 1976. Quantitative assessment of carcinogenic risks associated with "hot particles." *Nature* 259:535-39. [Also Central Electricity Generating Board report RD/B/N2878, April 1974.]
- McClellan, R. O. 1972. Progress in studies with transuranic elements at the Lovelace Foundation. *Health Phys.* 22:815-22.
- McClellan, R. O. 1981. Taped personal interview at Albuquerque, N. Mex., and brief history of Inhalation Toxicology Research Institute prepared as a personal communication by Dr. McClellan.
- McClellan, R. O., B. B. Boecker, R. V. Jones, J. E. Barnes, T. L. Chiffelle, C. H. Hobbs, and H. C. Redman. 1972. The toxicity of inhaled radiostrontium in experimental animals. In *Biomedical implications of radiostrontium exposure*, eds. M. Goldman and L. K. Bustad, CONF-710201, pp. 149-67. Proceedings of a symposium held in Davis, Calif., February 22-24, 1971. Springfield, Va.: National Technical Information Service.
- McGandy, R. B., A. R. Kennedy, M. Terzaghi, and J. B. Little. 1974. Experimental respiratory carcinogenesis: Interaction between alpha radiation and benzo(a)pyrene in the hamster. In *Experimental lung cancer: Carcinogenesis and bioassays*, eds. E. Karbe and J. F. Park, pp. 485-91. Proceedings of a symposium held in Seattle, Wash., June 23-26, 1974. New York: Springer-Verlag.
- Mercer, T. T. 1963. On the calibration of cascade impactors. *Ann. Occup. Hyg.* 6:1-14.
- Mercer, T. T. 1964. The stage constants of cascade impactors. *Ann. Occup. Hyg.* 7:115-24.
- Mercer, T. T. 1965. The interpretation of cascade impactor data. *Am. Ind. Hyg. Assoc. J.* 26:236-41.
- Mercer, T. T. 1967. On the role of particle size in the dissolution of lung burdens. *Health Phys.* 13:1211-21.
- Mercer, T. T. 1973. *Aerosol technology in hazard evaluation.* New York: Academic Press. [Am. Ind. Hyg. Assoc. Monograph.]
- Mercer, T. T. 1975. The deposition model of the task group on lung dynamics: A comparison with recent experimental data. *Health Phys.* 29:673-80.
- Mercer, T. T., P. E. Morrow, and W. Stöber, eds. 1972. Assessment of airborne particles: Fundamentals, applications, and implications to inhalation toxicity. In *Proceedings of a symposium held at the Univ. of Rochester.* Springfield, Ill.: Charles C. Thomas.
- Mercer, T. T., M. I. Tillery, and C. W. Ballew. 1962. *A cascade impactor operating at low volumetric flow rates.* LF-5. Albuquerque, N. Mex.: Lovelace Biomedical and Environmental Research Foundation, Fission Product Inhalation Project.

- Mercer, T. T., M. I. Tillery, and H. Y. Chow. 1968. Operating characteristics of some compressed-air nebulizers. *Am. Ind. Hyg. Assoc. J.* 29:66-78.
- Metallurgical Laboratory Monthly Report. April 1945a. *Report of Health Division*, CH-2904, May 1945, declassified March 1952.
- Metallurgical Laboratory Monthly Report. May 1945b. *Report of Health Division*, CH-2991, June 1945, declassified March 1957. [Especially Wender and Dailey, p. 12; Abrams and Seibert, p. 13.]
- Miller, C. E. and J. B. Corcoran. 1958. *The human spectrometer. II. Radium content of a Ra^{226} inhalation case 2300 days after exposure.* ANL-5967, pp. 129-34. Argonne, Ill.: Argonne National Laboratory.
- Morgan, K. Z. 1948. *An estimate of the exposure from specks of insoluble radioactive material that may become lodged in the lungs.* File No. CF-48-8-86, August 2, 1948, declassified September 15, 1955. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Morken, D. A. and P. E. Morrow. 1956. *The control and measuring systems of an apparatus for the study of respiratory tract retention.* UR-415. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Morken, D. A. and R. H. Wilson. 1960. *A four-channel continuously recording monitor for air-borne radioactivity.* UR-576. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Morrow, P. E. 1960. Some physical and physiological factors controlling the fate of inhaled substances—I. Deposition. *Health Phys.* 2:366-78.
- Morrow, P. E. 1964. Evaluation of inhalation hazards based upon the respirable dust concept and the philosophy and application of selective sampling. *Am. Ind. Hyg. Assoc. J.* 25:213-36.
- Morrow, P. E. 1970. Models for the study of particle retention and elimination in the lung. In *Inhalation carcinogenesis*, eds. M. G. Hanna, Jr., P. Nettesheim, and J. R. Gilbert, CONF-691001, pp. 103-19. Proceedings of a conference held in Gatlinburg, Tenn.: October 8-11, 1969. Springfield, Va.: National Technical Information Service.
- Morrow, P. E. 1972. Lymphatic drainage of the lung in dust clearance. *Ann. N.Y. Acad. Sci.* 200:46-65.
- Morrow, P. E. 1977. Clearance kinetics of inhaled particles. In *Respiratory defense mechanisms. II.*, ed. J. D. Brain et al., vol. 5 of *Lung biology in health and disease*, pp. 491-541. New York: Dekker.
- Morrow, P. E. and L. J. Casarett. 1955. *An experimental approach to the study of the respiratory deposition and retention of certain alpha emitters.* UR-308. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Morrow, P. E. and L. J. Casarett. 1961. An experimental study of the deposition and retention of a plutonium-239 dioxide aerosol. In *Inhaled particles and vapours*, ed. C. N. Davies, pp. 167-77. Proceedings of an international symposium held in Oxford, March 24-April 1, 1960. London: Pergamon Press.
- Morrow, P. E. and R. J. Della-Rosa. 1956. *The fate of polonium-210 colloid and polonium-210 tagged silver particles following intratracheal administration to rabbits.* UR-478. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Morrow, P. E. and R. J. Della Rosa. 1964. Distribution and excretion of polonium-210. VII. Fate of polonium colloid after intratracheal administration to rabbits. *Radiat. Res. Suppl.* 5:124-32.
- Morrow, P. E., F. R. Gibb, and H. D. Beiter. 1972. Inhalation studies of uranium trioxide. *Health Phys.* 23:273-80.
- Morrow, P. E., F. R. Gibb, and L. J. Leach. 1966. The clearance of uranium dioxide dust from the lungs following single and multiple inhalation exposures. *Health Phys.* 12:1217-23.
- Morrow, P. E. and T. T. Mercer. 1964. A point-to-plane electrostatic precipitator for particle size sampling. *Am. Ind. Hyg. Assoc. J.* 25:8-14.
- Morrow, P. E. and R. E. Vosteen. 1953. Pneumotachographic studies in man and dog incorporating a portable wireless transducer. *J. Appl. Physiol.* 5:348-60.
- Morrow, P. E., F. R. Gibb, H. Davies, J. Mitola, D. Wood, N. Wraight, and H. S. Campbell. 1967. The retention and fate of inhaled plutonium dioxide in dogs. *Health Phys.* 13:113-33.
- Morrow, P. E., E. Mehrhof, L. J. Casarett, and D. A. Morken. 1958. An experimental study of aerosol deposition in human subjects. *AMA Arch. Ind. Health* 18:292-98.
- Moskalev, Yu. I. 1966. Distribution and biological effects of radioactive isotopes. Atomizdat, Moscow. AEC-tr-6944 (rev). U. S. Atomic Energy Commission, Division of Technical Information.

- Moss, W. D., E. C. Hyatt, and H. F. Schulte. 1961. Particle size studies on plutonium aerosols. *Health Phys.* 5:212-18.
- Muggenburg, B. A., J. A. Mewhinney, F. F. Hahn, B. B. Boecker, R. A. Guilmette, C. H. Hobbs, J. L. Mauderly, R. O. McClellan, B. S. Merickel, D. L. Lundgren, J. A. Pickrell, and N. D. Stalnaker. 1979. Toxicity of inhaled alpha-emitting radionuclides—Status report. In *Inhalation Toxicology Research Institute annual report 1978-1979*. LF-69, pp. 117-21. Albuquerque, N. Mex.: Lovelace Biomedical and Environmental Research Foundation.
- Muir, J. R., B. R. Fish, N. L. Gillum, E. S. Jones, H. A. Ludeman, J. A. Payne, and J. L. Thompson. 1959. *Distribution and excretion of uranium*. ORNL-2806, p. 191. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Myers, D. S. 1972. A plea for consistent lung burden criteria for insoluble alpha emitting isotopes. *Health Phys.* 22:905-09.
- NAS-NRC. See National Academy of Sciences-National Research Council.
- National Academy of Sciences-National Research Council. 1961. *Effects of inhaled radioactive particles*. Report of Subcommittee on Inhalation Hazards of the Committee on Pathologic Effects of Atomic Radiation. Publ. 848. Washington, D.C.
- National Academy of Sciences-National Research Council. 1976. *Health effects of alpha-emitting particles in the respiratory tract*. Report of ad hoc committee of the Advisory Committee on Biological Effects of Ionizing Radiation. Washington, D.C.
- National Council on Radiation Protection and Measurements. 1975a. *Alpha-emitting particles in lungs*. Report no. 46. Washington, D.C.
- National Council on Radiation Protection and Measurements. 1975b. *Natural background radiation in the United States*. Report no. 45. Washington, D.C. [Report from a committee chaired by John Harley, HASL. Note especially chapter 6.]
- NCRP. See National Council on Radiation Protection and Measurements.
- Nelson, N. 1961. Radiation cancer of the lung: Tissue sensitivity and factors influencing dosage from airborne substances. In *Inhaled particles and vapours*, ed. C. N. Davies, pp. 221-30. Proceedings of an international symposium held in Oxford, March 29-April 1, 1960. London: Pergamon Press.
- Nettesheim, P., M. G. Hanna, Jr., D. G. Doherty, R. F. Newell, and A. Hellman. 1970. Effects of chronic exposure to artificial smog and chromium oxide dust on the incidence of lung tumors in mice. In *Inhalation carcinogenesis*, eds. M. G. Hanna, Jr., P. Nettesheim, and J. R. Gilbert, CONF-691001, pp. 305-20. Proceedings of a conference held in Gatlinburg, Tenn., October 8-11, 1969. Springfield, Va.: National Technical Information Service.
- New York University. 1974. Work of Pasternak and Harley in the 11th annual report from the New York Univ., Institute of Environmental Medicine, p. 13.
- NYU. See New York University.
- Pacific Northwest Laboratory. 1972. *Pacific Northwest Laboratory annual report for 1971 to the USAEC Division of Biology and Medicine*, vol. 1, Life sciences, pt. 1, Biological sciences, pp. v-xii. BNWL-1650, pt. 1, Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Park, J. F., W. J. Bair, and R. H. Busch. 1972. Progress in beagle dog studies with transuranium elements at Battelle-Northwest. *Health Phys.* 22:803-10.
- Park, J. F., E. B. Howard, and W. J. Bair. 1970. Acute toxicity of inhaled $^{238}\text{PuO}_3$ in beagles. In *Pacific Northwest Laboratory annual report for 1968 to the USAEC Division of Biology and Medicine*. Vol. 1 Life sciences, Part 1 Biological sciences. BNWL-1050, pt. 1, pp. 3.6-3.13. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Park, J. F. (principal investigator), G. A. Apley, A. C. Case, D. L. Catt, G. E. Dagle, T. C. Kinnas, G. J. Powers, H. A. Ragan, S. E. Rowe, R. E. Schirmer, D. L. Stevens, C. R. Watson, R. E. Weller, and E. L. Wierman. 1982. Inhaled plutonium dioxide in dogs. In *Pacific Northwest Laboratory annual report for 1981 to the DOE Office of Energy Research. Part 1 Biomedical sciences*. PNL-4100, pt. 1, pp. 61-71. Richland, Wash.: Pacific Northwest Laboratory.
- Park, J. F., E. B. Howard, B. O. Stuart, A. P. Wehner, and J. V. Dilley. 1970. Cocarcinogenic studies in pulmonary carcinogenesis. In *Morphology of experimental respiratory carcinogenesis*, eds. P. Nettesheim, M. G. Hanna, Jr., and J. W. Deatherage, Jr., CONF-700501, pp. 417-36. Proceedings of a conference held in Gatlinburg, Tenn., May 13-16, 1970. Springfield, Va.: National Technical Information Service.
- Parker, H. M. 1946. *Review of air monitoring procedures at Clinton Laboratories*. AEC report MDDC-471, declassified November 1946.

- Parsont, M. A., W. L. Holley, and W. D. Burnett. 1972. The effect of particle size on organ distribution of radioactive material deposited in the lungs. *Health Phys.* 22:143-48.
- Pfleger, R. C., B. B. Boecker, H. C. Redman, J. A. Pickrell, J. L. Mauderly, R. K. Jones, S. A. Benjamin, and R. O. McClellan. 1975. Biological alterations resulting from chronic lung irradiation. I. The pulmonary lipid composition, physiology and pathology after inhalation by beagle dogs of ^{144}Ce -labeled fused clay aerosols. *Radiat. Res.* 63:275-98.
- Phalen, R. F. and P. E. Morrow. 1973. Experimental inhalation of metallic silver. *Health Phys.* 24:509-18.
- Pickrell, J. A., D. V. Harris, R. C. Pfleger, S. A. Benjamin, J. J. Belasich, R. K. Jones, and R. O. McClellan. 1975. Biological alterations resulting from chronic lung irradiation. II. Connective tissue alterations following inhalation of ^{144}Ce fused clay aerosol in beagle dogs. *Radiat. Res.* 63:299-309.
- PNL. See Pacific Northwest Laboratory.
- Raabe, O. G. 1970. Generation and characterization of aerosols. In *Inhalation carcinogenesis*, eds. M. G. Hanna, Jr., P. Nettesheim, and J. R. Gilbert, CONF-691001, pp. 123-72. Proceedings of a conference held in Gatlinburg, Tenn., October 8-11, 1969. Springfield, Va.: National Technical Information Service.
- Raabe, O. G. 1972. Instruments and methods for characterizing radioactive aerosols. *IEEE transactions on nuclear science*. NS-19(1):64-75.
- Redman, H. C., A. J. Wilson, S. W. Bielfelt, and R. O. McClellan. 1970. Beagle dog production experience at the fission product inhalation program (1961-1968). *Lab. Anim. Care* 20:61-68.
- Richmond, C. R. 1975. The importance of non-uniform dose-distribution in an organ. *Health Phys.* 29:525-37.
- Richmond, C. R. 1976. *Current status of the plutonium hot-particle problem*. NS 17(4) V A-1. Washington, D.C.: U.S. Department of Energy, Division of Biomedical and Environmental Research.
- Richmond, C. R., J. Langham, and R. S. Stone. 1970. Biological response to small discrete highly radioactive sources. II. Morphogenesis of microlesions in rat lungs from intravenously injected $^{239}\text{PuO}_2$ microspheres. *Health Phys.* 18:401-08.
- Ross, D. M. 1962. Memorandum and draft report from D. M. Ross to Lester R. Rogers, Assistant Director for Materials Standards, Division of Licensing and Regulation, USAEC, March 30, 1962.
- Ross, D. M. 1980. Personal interview at Germantown, Md., March 1980.
- Rothstein, A. and A. Hayes. 1957. *A unit for exposing animals to radioactive dusts*. UR-309. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Rundo, J. and J. Sedlet. 1973. Retention and elimination of berkelium-249—californium-249 following acute accidental inhalation. In *Proceedings of the 3d international congress of the International Radiation Protection Association*, ed. W. S. Snyder, CONF-730907-P1, pp. 731-35. Held in Washington, D.C., September 9-14, 1973. Oak Ridge, Tenn.: Technical Information Center.
- Sanders, C. L. 1969a. The biological behavior of $^{239}\text{PuO}_2$ particles: Role of the peritoneal mononuclear phagocyte. *Radiat. Res.* 38:125-39.
- Sanders, C. L. 1969b. The distribution of inhaled plutonium-239 dioxide particles within pulmonary macrophages. *Arch. Environ. Health* 18:904-12.
- Sanders, C. L. 1972. Deposition patterns and the toxicity of transuranium elements in lung. *Health Phys.* 22:607-15.
- Sanders, C. L. 1974. Toxicology of inhaled $^{238}\text{PuO}_2$, $^{239}\text{PuO}_2$ and $^{244}\text{CmO}_x$ in the rat. High dose effects. In *Pacific Northwest Laboratory annual report for 1973 to the USAEC Division of Biomedical and Environmental Research. Part 1. Biological sciences*. BNWL-1850, pt. 1, pp. 56-59. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Sanders, C. L. 1975. Toxicology of inhaled $^{239}\text{PuO}_2$ in rats. Progress report. In *Pacific Northwest Laboratory annual report for 1974 to the USAEC Division of Biomedical and Environmental Research. Part 1. Biological sciences*. BNWL-1950, pt. 1, pp. 28-30. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Sanders, C. L., D. K. Craig, and V. H. Smith. 1974. Early fate of inhaled $^{238}\text{PuO}_2$, $^{239}\text{PuO}_2$, and $^{244}\text{CmO}_x$ in rats. In *Pacific Northwest Laboratory annual report for 1973 to the USAEC Division of Biomedical and Environmental Research. Part 1. Biological sciences*. BNWL-1850, pt. 1, pp. 54-56. Richland, Wash.: Battelle, Pacific Northwest Laboratories.

- Sanders, C. L. and G. E. Dagle. 1974. Studies of pulmonary carcinogenesis in rodents following inhalation of transuranic compounds. In *Experimental lung cancer: Carcinogenesis and bioassays*, eds. E. Karbe and J. F. Park, pp. 422-29. Proceedings of a symposium held in Seattle, Wash., June 23-26, 1974. New York:Springer-Verlag.
- Sanders, C. L., Jr., R. C. Thompson, and W. J. Bair. 1970. Lung cancer: Dose response studies with radionuclides. In *Inhalation carcinogenesis*, eds. M. G. Hanna, Jr., P. Nettesheim, and J. R. Gilbert, CONF-691001, pp. 285-303. Proceedings of a conference held in Gatlinburg, Tenn., October 8-11, 1969. Springfield, Va.: National Technical Information Service.
- Sanders, C. L., R. R. Adey, K. Rhoads, and R. M. Madison. 1977. Life history of plutonium dioxide in the lung: From macrophage to carcinoma. In *Pulmonary macrophage and epithelial cells*, eds. C. L. Sanders, R. P. Schneider, G. E. Dagle, and H. A. Ragan, CONF-760927, pp. 451-62. Proceedings of the 16th annual Hanford biology symposium held in Richland, Wash., September 27-29, 1976. Springfield, Va.: National Technical Information Service.
- Sanders, C. L. (principal investigator), J. A. Mahaffey, and K. E. McDonald. 1982. Low level ^{239}Pu life-span studies. In *Pacific Northwest Laboratory annual report for 1981 to the DOE Office of Energy Research. Part 1 Biomedical sciences*. PNL-4100, pt. 1, 1982, pp. 89-91. Richland, Wash.: Pacific Northwest Laboratory.
- Sapirie, S. R. 1966. Memorandum from S. R. Sapirie, Manager, Oak Ridge Operations to C. L. Dunham, Director, Division of Biology and Medicine, AEC Headquarters. Subject: Process-produced uranium aerosols—Recommendation for inhalation research. [Memorandum not dated, but internal transmittal dated July 22, 1966.]
- Schneider, R. P. and A. M. Robinson. 1978. In vitro studies of actinides and alveolar macrophages. In *Pacific Northwest Laboratory annual report for 1977 to the DOE Assistant Secretary for Environment. Part 1 Biomedical sciences*. PNL-2500, pt. 1, pp. 3.52-3.53. Richland, Wash.: Pacific Northwest Laboratory.
- Schulte, H. F. 1967. *Personal air sampling and multiple stage sampling: Interpretation of results from personnel and static air samplers*. Paper presented at a symposium on radiation dose measurements. Stockholm: European Nuclear Energy Agency.
- Scott, J. K. and R. G. Thomas. 1957. *Induction of pulmonary tumors following intratracheal injection of polonium-210*. Quarterly review, July-September 1957. Rochester, N.Y.: University of Rochester Atomic Energy Project.
- Scott, K. G., D. Axelrod, J. Crowley, and J. G. Hamilton. 1949. Deposition and fate of plutonium, uranium and their fission products inhaled as aerosols by rats and man. *Arch. Pathol.* 48:31-54.
- Scott, K. G., D. Axelrod, J. Crowley, H. C. Lanz, Jr., and J. G. Hamilton. 1945. *Studies on the inhalation of fissionable materials and fission products and their subsequent fate in rats and mice*. Metallurgical Laboratory Report CH-3590, AEC report MDDC-1276, December 1945, declassified August 1947.
- Seaborg, G. T. 1973. Medical uses: Americium-241; californium-252. Chapter 21 in *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh, pp. 929-40. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.
- Seibert, H. C. and R. Abrams. Undated. *Acute toxicity of inhaled 275 day Ce^{144}* . AEC report MDDC-329, declassified September 1946.
- Silverman, L., C. E. Billings, and M. W. First. 1971. *Particle size analysis in industrial hygiene*. New York: Academic Press.
- Smith, D. M., E. C. Anderson, J. R. Prine, L. M. Holland, and C. R. Richmond. 1976. Biological effect of focal alpha radiation of the hamster lung. In *Biological and environmental effects of low-level radiation*, STI/PUB/409, vol. 2, pp. 121-29. Proceedings of a symposium held in Chicago, November 3-7, 1975. Vienna: International Atomic Energy Agency.
- Smith, D. M., R. G. Thomas, and E. C. Anderson. 1980. Respiratory tract carcinogenesis induced by radionuclides in the Syrian hamster. In *Pulmonary toxicology of respirable particles*, eds. C. L. Sanders, F. T. Cross, G. E. Dagle, and J. A. Mahaffey, DOE CONF-791002, pp. 575-90. Proceedings of the 19th annual Hanford life sciences symposium held in Richland, Wash., October 22-24, 1979. Springfield, Va.: National Technical Information Service.
- Smith, F. A., R. J. Della Rosa, and L. J. Casarett. 1955. *Analytical and autoradiographic methods for polonium*. UR-305. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.

- Smith, F. A., P. E. Morrow, F. R. Gibb, R. J. Della Rosa, L. J. Casarett and J. K. Scott. 1960. *Distribution and excretion studies in dogs exposed to an aerosol containing polonium-210*. UR-566. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project. [Also *Am. Ind. Hyg. Assoc. J.* 22:201-08 (1961), with D. A. Morken and J. N. Stannard.]
- Smith, G. A., R. G. Thomas, and J. K. Scott. 1960. The metabolism of indium after administration of a single dose to the rat by intratracheal subcutaneous, intramuscular and oral injection. *Health Phys.* 4:101-08.
- Snipes, M. B., B. B. Boecker, and R. O. McClellan. 1983. Retention of monodisperse or polydisperse aluminosilicate particles inhaled by dogs, rats, and mice. *Toxicol. Appl. Pharmacol.* 69:345-62.
- Stannard, J. N. 1959. An evaluation of inhalation hazards in the nuclear energy industry. In *Proceedings of the 2nd United Nations international conference on the peaceful uses of atomic energy*, vol. 1, pp. 40-51. Held in Geneva, September 1-13, 1958. Geneva: United Nations.
- Stannard, J. N. 1973. Plutonium in the environment. Chapter 15 in *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh, pp. 669-88. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.
- Stannard, J. N. 1975. The concepts of critical organ and radiation dose as applied to plutonium. *Health Phys.* 29:539-50.
- Stannard, J. N. and P. E. Morrow. 1956. Retention of sub-micronic aerosols in the human respiratory tract. In *The shorter-term biological hazards of a fallout field*, eds. G. M. Dunning, and J. A. Hilcken, pp. 189-95. Proceedings of a symposium held December 12-14, 1956. Washington, D.C.: U.S. Atomic Energy Commission.
- Stöber, W. 1967. Design and performance of a size-separating aerosol centrifuge facilitating particle size spectrometry in the submicron range. In *Assessment of airborne radioactivity*, pp. 393-404. Vienna: International Atomic Energy Agency.
- Stroud, A. N. 1977. Chromosome aberrations induced in Syrian hamster lung cells by inhaled $^{238}\text{PuO}_2$ - ZrO_2 particles. *Radiat. Res.* 69:583-90.
- Stuart, B. O. 1970. Comparative distribution of ^{238}Pu and ^{239}Pu in rats following inhalation of the oxide. *Pacific Northwest Laboratory annual report for 1968 to the USAEC Division of Biology and Medicine. Vol. 1 Life sciences, Part 1 Biological sciences*. BNWL-1050, pt. 1, pp. 3.19-3.20. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Stuart, B. O. 1973. Deposition of inhaled aerosols. *Arch. Intern. Med.* 131:60-73.
- Stuart, B. O. 1976. Deposition and clearance of inhaled particles. *Environ. Health Perspect.* 16:41-53.
- Stuart, B. O. and T. M. Beasley. 1967. Non-equilibrium tissue distributions of uranium and thorium following inhalation of uranium ore by rats. In *Inhaled particles and vapours. II.*, ed. C. N. Davies, pp. 291-98. Proceedings of an international symposium held in Cambridge, England, September 28-October 1, 1965. Oxford-London-New York: Pergamon Press.
- Stuart, B. O., P. J. Dionne, and W. J. Bair. 1971. Computer simulation of the retention and translocation of inhaled $^{239}\text{PuO}_2$ in beagle dogs. In *Pacific Northwest Laboratory annual report for 1970 to the USAEC Division of Biology and Medicine, Vol. 1. Life sciences, Part 1 Biological sciences*. BNWL-1550, pt. 1, pp. 66-68. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Stuart, B. O., W. J. Bair, W. J. Clarke, and E. B. Howard. 1968. *Acute toxicity of inhaled plutonium oxide-238 and -239 in rats*. AFWL-TR-68-49. Kirtland Air Force Base, N. Mex.: Air Force Weapons Laboratory.
- Tamplin, A. and T. Cochran. 1974. *Radiation standards for hot particles: A report on the inadequacy of existing radiation protection standards related to internal exposure of man to insoluble particles of plutonium and other alpha-emitting hot particles*. Washington, D.C.: Natural Resources Defense Council, Inc.
- Task Group on Lung Dynamics. 1966. Deposition and retention models for internal dosimetry of the human respiratory tract. *Health Phys.* 12:173-207.
- Taylor, D. M. 1973a. Chemical and physical properties of plutonium. Chapter 9 in *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh, pp. 323-47. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.

- Taylor, D. M. 1973b. Other plutonium isotopes. [Part III of chapter 10 on Distribution, excretion and effects of plutonium as a bone-seeker by J. Vaughan.] In *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard and J. B. Hursh, pp. 392-96. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.
- Taylor, L. S. 1984. *The Tri-Partite conferences on radiation protection, Canada, United Kingdom, United States (1949-1953)*. NVO-271. Springfield, Va.: National Technical Information Service.
- TGLD. See Task Group on Lung Dynamics.
- Thomas, R. G. 1957. *Metabolism of thorium-230 (ionium) administered by intratracheal injection to the rat*. UR-480. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Thomas, R. G. 1964a. Influence of aerosol parameters and the respiratory pattern upon hazards evaluation following inhalation exposure. In *Assessment of radioactivity in man*, vol. 1, pp. 355-68. Proceedings of a symposium held in Heidelberg, May 11-16, 1964. Vienna: International Atomic Energy Agency.
- Thomas, R. G. 1964b. Influence of aerosol properties upon gross distribution and excretion. *Health Phys.* 10:1013-28.
- Thomas, R. G. 1970. Estimation of ^{241}Am body burdens by analysis of whole-body scanning, excreta, and body weight data. *Health Phys.* 19:751-55.
- Thomas, R. G. 1976. Uptake kinetics of relatively insoluble particles by tracheobronchial lymph nodes. In *Radiation and the lymphatic system*, ed. J. E. Ballou, CONF-740930, pp. 67-72. Proceedings of the 14th annual Hanford biology symposium held in Richland, Wash., September 30-October 2, 1974. Springfield, Va.: National Technical Information Service.
- Thomas, R. G., R. O. McClellan, R. L. Thomas, T. L. Chiffelle, C. H. Hobbs, R. K. Jones, J. L. Mauderly, and J. A. Pickrell. 1972. Metabolism, dosimetry and biological effects of inhaled ^{241}Am in beagle dogs. *Health Phys.* 22:863-71.
- Thomas, R. G. and R. Lie. 1963. *Procedures and equipment used in inhalation studies on small animals*. LF-11. Albuquerque, N. Mex.: Lovelace Biomedical and Environmental Research Foundation, Fission Product Inhalation Project.
- Thomas, R. G. and D. M. Smith. 1979a. Lung tumors from $\text{PuO}_2\text{-ZrO}_2$ aerosol particles in Syrian hamsters. *Int. J. Cancer* 24:594-99.
- Thomas, R. G. and D. M. Smith. 1979b. Respiratory tract tumors in Syrian hamsters following inhalation of Pu-ZrO_2 particles. In *Biological implications of radionuclides released from nuclear industries*, STI/PUB/522, vol. 1, pp. 61-74. Proceedings of a symposium held in Vienna, March 26-30, 1979. Vienna: International Atomic Energy Agency.
- Thomas, R. G., D. M. Smith, and E. C. Anderson. 1980. Pulmonary carcinogenesis from plutonium-containing particles. In *Radiation protection: A systematic approach to safety*, vol. 2, pp. 131-34. Proceedings of the 5th congress of the International Radiation Protection Association held in Jerusalem, March 9-14, 1980. Oxford-New York: Pergamon Press.
- Thomas, R. G. and J. N. Stannard. 1956. *The metabolism of polonium-210 administered by intratracheal injection to the rat*. UR-430. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Thomas, R. G. and J. N. Stannard. 1964. Distribution and excretion of polonium-210. VI. After intratracheal administration in the rat. *Radiat. Res. Suppl.* 5:106-23. [Univ. of Rochester Atomic Energy Project Report UR-605.]
- Thomas, R. G., S. A. Walker, and R. O. McClellan. 1971. Relative hazards for inhaled ^{95}Zr and ^{95}Nb particles formed under various thermal conditions. *Proc. Soc. Exp. Biol. Med.* 138:228-34.
- Thomas, R. G., S. W. Felicetti, R. V. Lucchino, and R. O. McClellan. 1973. Retention patterns of antimony in mice following inhalation of particles formed at different temperatures. *Proc. Soc. Exp. Biol. Med.* 144:544-50.
- Tombropoulos, E. G., J. G. Hadley, J. M. Thomas, and D. K. Craig. 1977. Biochemical effects of inhaled $^{239}\text{PuO}_3$ on lung lipids. *Health Phys.* 32:111-13.
- Toribara, T. Y., C. Predmore, and P. A. Hargrave. 1962. *The separation and determination of plutonium in diverse biological samples*. UR-606. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Voegtlin, C. and H. C. Hodge. 1949. *Pharmacology and toxicology of uranium compounds*. National Nuclear Energy Series, div. VI, vol. 1 (pts. I and II). New York: McGraw-Hill.

- Voegtlin, C. and H. C. Hodge. 1953. *Pharmacology and toxicology of uranium compounds, chronic inhalation and other studies*. National Nuclear Energy Series, div. VI, vol. 1 (pts. III and IV). New York: McGraw-Hill.
- Wager, R. W. and L. A. Temple. 1955. Toxicity of radioactive particles. I. Intratracheal injection of radioactive suspensions. In *Biology research—Annual report 1954*, HW-35917, pp. 156-66. Richland, Wash.: Hanford Works.
- Wager, R. W., N. L. Dockum, L. A. Temple, and D. H. Willard. 1956. Toxicity of radioactive particles. IA. Intratracheal injection of radioactive suspensions. In *Biology research—Annual report 1955*, HW-41500, pp. 61-72. Richland, Wash.: Hanford Works.
- Warren, S. and O. Gates. 1940. Radiation pneumonitis. Experimental and pathologic observations. *Arch. Pathol.* 30:440-60.
- Warren, S. and O. Gates. 1968. Cancers induced in different species by continuous γ -radiation. *Arch. Environ. Health* 17:697-704.
- West, C. M. and L. M. Scott. 1969. Uranium cases showing long chest burden retention—An updating. *Health Phys.* 17:781-91.
- Whipple, G. H., J. N. Stannard, G. J. Miller, M. L. Ingram, and T. T. Mercer. 1955. *Personnel protection in the radioactive inhalation program*. UR-310. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Willard, D. H. and W. J. Bair. 1958. Behavior of I^{131} following its inhalation as a vapor and as a particle. HW-58221. Richland, Wash.: Hanford Atomic Products Operation.
- Willard, D. H. and W. J. Bair. 1961. Behavior of I^{131} following its inhalation as a vapor and as a particle. *Acta Radiol.* 55:486-96.
- Willard, D. H., L. A. Temple, and W. J. Bair. 1957. Turnover and tissue distribution of radio-ruthenium oxide in the lungs of mice. HW-52286. Richland, Wash.: Hanford Atomic Products Operation.
- Williamson, W. Jr. 1957. *Investigation and correlation of some physical parameters of fallout material*. USNRDL-TR-152. Washington, D.C.: U.S. Naval Radiological Defense Laboratory.
- Wilson, H. B., G. E. Sylvester, S. Laskin, C. W. LaBelle, J. K. Scott, and H. E. Stokinger. 1955. Relation of particle size of U_3O_8 dust to toxicity following inhalation by animals. *AMA Arch. Ind. Health* 11:11-16.
- Wilson, H. B., G. E. Sylvester, S. Laskin, C. W. LaBelle, and H. E. Stokinger. 1948. The relation of particle size of uranium dioxide dust to toxicity following inhalation by animals. Preliminary report. *J. Ind. Hyg. Toxicol.* 30:319-31.
- Wilson, R. H., W. F. Neuman, A. Rothstein, and J. K. Scott. 1955. *Physical plant for a radioactive inhalation laboratory*. UR-302. Rochester, N.Y.: Univ. of Rochester Atomic Energy Project.
- Winters, T. H. and J. R. Di Franze. 1982. Radioactivity in cigarette smoke. *N. Eng. J. Med.* 306:364-65.
- Wright, B. M. 1950. A new dust-feed mechanism. *J. Sci. Instrum.* 27:12-15.
- Yeh, H. C. 1980. *Respiratory tract deposition models—Final report*. LF-72. Albuquerque, N. Mex.: Lovelace Biomedical and Environmental Research Foundation, Inhalation Toxicology Research Institute.
- Yuile, C. L., H. L. Berke, and T. Hull. 1967. Lung cancer following polonium-210 inhalation in rats. *Radiat. Res.* 31:760-74.
- Yuile, C. L., F. R. Gibb, and P. E. Morrow. 1970. Dose-related local and systemic effects of inhaled plutonium-238 and plutonium-239 dioxide in dogs. *Radiat. Res.* 44:821-34.

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(a) The radionuclides considered in this chapter move very freely in the environment and living organisms. Therefore, there is little difference between inhalation and other routes. For this reason the chapter reviews work by several routes of administration since they apply to inhalation problems as well.

1. *Chlorophyll a* (Chl *a*)

[illegible]

Capsule Chronology

- 1938 Tritium discovery announced by Alvarez and Cornog. Produced by accelerators.
- 1942 Failla calculates tolerance concentrations for radioactive gases in air. Consideration given to 5.4-day xenon in design of pilot plant for MED^(a) operations (Wollan and Stephenson, Met Lab).
- 1943 Radioxenon causes special concerns as possible off-gas from the Chicago pile. Abrams studies radioargon as surrogate for radioxenon. Hazards of inhaled iodine vapor recognized at Met Lab, Chicago. Hamilton indicates that inhaled ruthenium particles are much more hazardous than ⁷⁰Kr, ¹³¹I, or ¹²⁷Xe (Berkeley).
- 1944 Xenon exposure unit constructed and mice exposed at Clinton Labs (Cole). Dose to lung high, but effects minimal.
Experiments at Chicago with ¹³¹I (Daily, Wender, and Abrams). Idea generated for use of stable iodine to block thyroid uptake of iodine vapor (Berkeley).
- 1947 Work at Berkeley measures tissue contents of xenon after exposure.
- 1948 Brues and Buchanan expose mice to atmospheres of ¹⁴C (Argonne).

EARLY POSTWAR YEARS

- Hanford work on tritium and iodine vapor begins (Thompson and Ballou; Kornberg; Bustad; Bair); a major effort.
- Work on radioxenon continues, but attention focused more on radio-krypton (mostly ⁸⁵Kr). Several laboratories. Calculations indicate skin dose will exceed lung dose.
- Los Alamos work on inhalation and skin-absorption of tritium in man (Pinson, Langham). Skin absorption work at Hanford (Kornberg).
- Argonne work with ¹⁴C and tritium continued.
- Study of behavior of noble gases (stable) in man (Tobias at Berkeley).
- Early 1950s Large quantities of tritium found to be produced in fusion weapons explosions, far exceeding amounts produced in fission. Also, tritium assumes importance as an ingredient of the fusion devices, and special reactors are built to produce it.
- 1951 Jennings and Brues compare toxicity of tritium to that of x rays (Argonne).
- 1952 Further work by Brues on toxicity of tritium (Argonne).
- 1953 Concentrated work at Los Alamos on RBE of tritium (Furchner and Storer; later Spalding; Langham and Anderson; Worman).
- 1954 Los Alamos work on toxicity of tritium continues with animal exposures (Langham and Anderson).
- 1955 Libby identifies ¹⁴C in nature, estimates amount present.

(a) For abbreviations and acronyms, see Appendix D.

- 1955, 1957 Furchner, Anderson, et al.; Storer et al. (Los Alamos) work on acute effects of tritium.
- 1957 Comparison of tritium to ^{60}Co gamma rays given at an exponentially declining dose rate (Furchner at Los Alamos).
Windscale accident releases large quantities of radioiodine, much in vapor form (details in chapter 11).
Work on solubility of radon in body fat (Hursh and Nussbaum at Rochester); see chapter 3.
- 1958 Willard and Bair compare iodine vapor and silver iodide particles (Hanford).
- 1960s Growth of work with tritiated and iodinated macromolecules—see chapter 20 (M.D. Anderson Hospital, Brookhaven, Lawrence Livermore, Oak Ridge, Ohio State, Rochester).
Peculiar physiological effects of noble gases noted but at high partial pressures.
Experimental work at Savannah River on tritium in man (Reinig, Butler, Sanders, et al.).
- 1962 Federal Radiation Council considers inhalation of iodine vapor.
Berkeley work with tritium (Siri and Evers).
Richmond work on tritium (Los Alamos)—no actual inhalation studies.
- 1963 Hanford Biology Symposium includes papers on iodine vapor.
- 1965 Work with tritiated macromolecules shows they can produce cancer (Dewey et al. at M.D. Anderson).
- 1966 Canadian reports on behavior of tritium in man (Osborne).
- 1968 Snyder report of excretion rates and calculated doses in Oak Ridge employee who inhaled HTO.
- 1969 First reports of Cahill's work on tritium toxicity (Rochester and EPA, North Carolina). Includes effects on embryo and progeny over two generations (published in 1973). Possible synergistic effects with lead.
- 1970 Woodard's review of tritium (AEC series).
Lovelace work on iodine inhalation.
- 1970s Experimental work with krypton (Kirk at Rochester and BRH^(a); Ballou et al., Battelle; Ellis at Brookhaven). Early work concerns mostly kinetics of movement in tissues and body fluids. Later work turns to effects (Kirk, Rehnberg and Morken at Rochester and BRH).
Hanford work with krypton using rats, dogs, and sheep, both pharmacokinetics and effects. No tumors or other cancers induced in adults, but skin lesions occur in newborn rats and some became carcinomas. Reports continue into the 1980s and are still appearing (Ballou, Willard, et al.).
Brookhaven work on krypton reports on sixteen human subjects (Ellis et al.). Concentrates on metabolism.

(a) Later work was under EPA auspices.

- 1971 Tritium Symposium at Las Vegas, published 1973 (Moghissi and Carter, PHS-AEC-EPA).
- 1973 Bernard devises new models for ^{14}C (Oak Ridge).
Reports on Swiss luminizers (Seelentag). Two fatalities.
Also reports of urinary excretion of tritium in Czech luminizers (Houšková et al.).
- 1974 Evans's book on tritium (U.K.).
Anderson and Langham on acute toxicity of tritium (Los Alamos).
- Mid-1970s et seq. Brookhaven program on tritium (Carsten, Comerford, Cronkite, et al.). Very broad.
- 1975 Book on tritium by Moghissi and Carter. Includes work on luminizers who used tritium instead of radium (FDA auspices).
Life-span work with tritium in rats by Cahill (EPA, North Carolina). Includes possible behavioral effects and synergistic effects with lead.
Reactor Safety Study concludes that iodine vapor could be a significant hazard in a major reactor mishap (Rasmussen).
- 1976 Tritium compared to plutonium in producing chromosome aberrations (Blaylock and Trabalka at Oak Ridge).
Dobson's work on RBE for tritium compared to ^{60}Co gamma rays in short versus protracted exposures (Berkeley).
- 1977 Decided that internal doses (to thyroid) are much more important than external doses for iodines in vapor form.
Brookhaven work on tritium in biologically important molecules. See also chapter 20 (Bond, Carsten, Commerford, Cronkite, Feinendegan, et al.).
- 1978 IAEA symposium on tritium (published in 1979).
- 1979 NCRP report on tritium in the environment.
Oak Ridge work on genetic effects of tritium (Russell).
Review of tritium in Swiss watch industry.
Comparison of late effects of x ray, ^{137}Cs , and tritium (Carsten and Cronkite at Brookhaven).
- 1980 Book (by Davis) calculates thyroid doses as a function of age and mode of exposure. Inhalation sometimes, but not always, the critical mode.
NCRP report on ^{129}I .

Chapter 10

The Respirable Gases

Overview

The research reviewed in this chapter includes some of the most benign of the radioisotopes from a toxicological point of view (with the exception of iodine) and thus stands in sharp contrast to the inhaled particles we considered so exhaustively in the previous chapter. This difference is partly because they move freely and rapidly in and out of the body and tissues. There is relatively little tendency for long retention or the build-up of significant deposits. The difference is also partly because the radioelements concerned are, in general, low-energy beta emitters (again with the exception of iodine). And it is partly because some of the members of this group are almost inert chemically.

Nevertheless, the respirable gases have posed some unique problems that required experimental investigation. The effort during the Manhattan Engineer District days was relatively small next to some of the enormous efforts in other areas of pulmonary radiotoxicology. Yet it was important, especially the work on iodine.

When the fusion process was developed, tritium assumed considerable importance, and much research was necessary to determine the behavior of tritium as an element (T), as a gas (HT), and as tritiated water (HTO). It was also necessary to examine the toxicologic aspects of tritium when incorporated into biologically important molecules. The same applied to radioiodine and to radiocarbon.

In contrast to the large, highly organized projects in inhalation toxicology we saw in chapter 9, the research on the radioactive respirable gases was done more on an individual entrepreneur basis. Yet most of the work was carried out in government laboratories or on government contracts. Much of the iodine work started at Hanford. Tritium became a major activity at Argonne, Brookhaven, Los Alamos, the Environmental Protection Agency laboratories, and early at Hanford, with Rochester participating largely through graduate thesis projects.

The amount of scientifically interesting information derived from these researches (unfortunately treated very lightly herein) was almost in inverse ratio to the relative importance of these entities as exposure hazards. Yet, it is clear that it was important for both the researcher and the worker in industry to know what they were doing with even these mildly toxic radioactive substances.

I. Generalities

This second chapter on the inhalation toxicology of radioactive materials (pulmonary radiotoxicology) concerns materials and problems that stand in sharp contrast to the subjects of chapter 9. We deal here with elements that are either noble gases or that move freely enough in biological materials to have many of the characteristics of the noble gases. Although some of them form compounds of considerable importance, they are, for the most part, either broken down readily in the body or, for other reasons, exhibit considerable mobility. Consequently, retention times are characteristically short.^(a) We see little of the long-term residence in target organs, little of the formation of aggregates or colloids, little of the attachment to vector aerosols, and little of the other properties characteristic of inhaled particles. As a result of their mobility and their generally low-energy beta emissions, some of the most benign of the radionuclides from a toxicological point of view reside in this group.

Radioactive noble gases worthy of consideration are ^{41}Ar , isotopes of krypton, ^{222}Rn and ^{220}Rn , and the several isotopes of xenon. Other common radioactive substances that behave more or less like noble gases and fit the definition of respirable gas are iodine isotopes in vapor form, ^{14}C in carbon dioxide, and tritium as either tritium gas (^3H or T) or tritiated water ($^3\text{HO}_2$ or TO). All except radon and iodine have low-energy beta-particle emissions. The iodine beta can be considered as of intermediate energy.

Radon was discussed in chapter 3, although not much emphasis was placed on its behavior as a noble gas because of the importance of its radioactive daughter products. The others will be considered in the sections that follow, first in connection with the rather sparse work during the days of World War II and, later, on an individual basis in the years of growing concern and knowledge of their biomedical significance and behavior. Environmental behavior and problems of primary concern to ecosystems will be taken up in later chapters.

We will concentrate on the behavior and effects of these respirable gases on inhalation by mammalian species. However, many are so readily absorbed from the gastrointestinal tract, even the skin in some instances, that information gained using these other routes of administration can be applied as well to the inhalation route. Exceptions are where specific compounds of importance primarily in nuclear medicine are involved.

There have been no major projects built around these elements and compounds. Work was diffused (like the gases themselves) among a number of laboratories. There have been no major centers of action comparable to those we saw in chapter 9, although some individual investigators have concentrated their research in these areas. For this reason, we will arrange our discussion around the elements and the associated problems rather than laboratories.

II. The Respirable Gases in the Manhattan District Days

A. Noble Gases

We pointed out at the beginning of chapter 9 that the first biological experiments in the Manhattan Engineer District (MED) with inhaled materials of any

(a) Exceptions occur, as for example the labeled precursors of the nucleic acids, but they are not very important for inhaled gases. The chief exception is iodine in the thyroid.

kind concerned radioactive xenon. The concern for xenon arose from its production in reactors and the lack of easy means to trap it.

As part of an early Metallurgical Project monthly report from Chicago, Wollan and Stephenson (1942) discuss the amounts of "5.4-day"^(a) xenon (^{133}Xe) to be expected with operation of "The Pilot Plant" for one month and chemical processing of the products. The amount was 3×10^4 Ci, an amount that gave pause to those planning health protection in those early days. They calculated that man could safely breathe air having a concentration of this xenon isotope of 8×10^{-9} Ci/cm³. Thus, the 3×10^4 Ci produced would require 4×10^{12} cm³ of diluting air to bring the off-gases to this safe level. The Chicago workers concluded that this amount of dilution was feasible, but it had to be kept in mind.

In the same report, plans are mentioned for an apparatus to expose guinea pigs to radioactive gas, largely radioxenon, in Abbott Hall on the campus at the University of Chicago. In a report dated February 1943, the activities of K. S. Cole at Chicago with ^{127}Xe (36.4-day half-life) are described. These included attempts to determine ratios of effectiveness of radioxenon to fast neutrons and x rays. This work was built around materials expected to be released in the cooling air from the Clinton pile, but it seems also to have been aimed at experiments to be performed at Argonne (Stone 1943). Later in this same report, Cole reports on guinea pigs kept in radioxenon (^{127}Xe) at 0.1 mCi or 0.5 mCi/l. Although some of the animals died, dehydration, hypoxia, and other complications made it impossible to separate out any radiation effects. (The exposures were relatively short.)

By the May 1943 monthly report, R. Abrams (see chapter 9) was on the job at Chicago. Because radioactive xenon (i.e., ^{133}Xe) was not yet available in sufficient quantity, he substituted radioargon (^{41}Ar). This has a higher energy and shorter half-life than the xenon isotopes of interest at the time, but it was considered a reasonable substitute. Guinea pigs were given single exposures to progressively higher concentrations of ^{41}Ar in a bottle. Little biological effect ensued, which is not surprising since the total lung dose was between 1 and 2 r (Abrams 1943b). Similarly, no effect was seen after five exposures to ^{41}Ar at 300 mCi total dose (Abrams 1943a).^(b)

In August of 1943, a "Conference on Xenon Factor" was reported, which apparently took place at Chicago. This had little biomedical import except to close with a query as to how soon rabbits could be exposed to the products of "Cooper's solution process." In the monthly report for the same month, we find that a guinea pig exposed to 1.25×10^{-5} Ci/cm³ of ^{127}Xe died on the twenty-fifth day with average beta exposure to lung at 450 r. The cause of death was unknown. There was also some work reported on the possible use of gas mask canisters for removal of xenon from inhaled air. They appeared to be reasonably effective.

In the report for the month ending April 25, 1944, Cole (1944) tells of a unit installed at Clinton Labs for producing ^{133}Xe and the exposure of twelve mice. The highest activity concentration was 10^{-5} Ci/cm³, and the mouse receiving the

(a) The current figure for the half-life of ^{133}Xe is 5.245 days.

(b) Argon-41 is produced by neutron bombardment of normal atmospheric argon and was especially prevalent in early single-pass air-cooled reactors. Its short half-life (1.8 hr) and ease of dilution with the cooling air soon removed it from biomedical concern as a hazard.

longest exposure attained an average lung dose of 6,500 r^(a) (whole-body dose about 200 r). Six animals received 2,800 r to the bronchi and lungs over a period of 3.5 wk. They report no evidence of histological damage but do not indicate whether or not any significant time was allowed for effects to develop—probably not.

Subsequent Metallurgical Project reports were in the same vein insofar as work at Chicago was concerned. They continued to have trouble getting enough xenon for a good toxicological experiment.^(b) By the time they did get enough xenon, it was becoming apparent that other radionuclides posed much greater problems.

This view was probably based in part upon a letter from Joe Hamilton at Berkeley to C. M. Cooper in Chicago (Hamilton 1943a). By now (see chapter 6), the Berkeley group had prepared ⁷⁹Kr, ¹³¹I, ¹²⁷Xe, and a number of nongaseous fission products from material bombarded in the Berkeley cyclotron (Hamilton 1943b). To emphasize the relative importance of radioruthenium over some of the other nuclides, Hamilton states (as quoted in chapter 6), "I should like to point out in the first place that under these circumstances^(c) radio-ruthenium. . . is far more of a potential hazard than either the 8 day iodine or the 5 day xenon, since these elements have relatively short half-lives and their abundance at the time of chemical extraction may be many times less than that of the ruthenium" (Hamilton 1943a, p. 1). He goes on to cite preliminary results of experiments that show much longer retention of ruthenium in the lung than of either radioxenon or radioiodine. Hamilton's admonition was appropriate to the time when major new problems had to be addressed.

The Berkeley work tied closely to work being done in John Lawrence's laboratory on the behavior of the radioactive noble gases in human subjects. A direct determination of the xenon content of animal tissues was reported in work declassified in 1947 (Hamilton 1947). Rats were put into a desiccator with 2 mCi of ¹²⁷Xe^(d) in the gas phase with oxygen renewed by a bubbling device. After sixteen hours' exposure, the tissues were analyzed with precautions to lose as little xenon as possible. The gamma rays from the xenon were measured through the walls of the glass vials containing the tissues in paraffin. As expected, the tissues with the most fat had the most xenon. Figures are given for sixteen tissues and whole body. This led to determination of oil-to-water solubility ratios of a number of inert gases available as radioactive isotopes and the conclusion that differential uptake curves of xenon versus krypton or ⁴¹Ar provided a means of measuring the relative amounts of watery and fatty tissues in different individuals.

Radioactive krypton (⁸⁵Kr) has a half-life of 10.27 yr, a low-energy beta particle emission of $E = 0.250$ MeV, and a fission yield of 3×10^{-2} atoms per fission, high relative to many other fission products. However, it is so unreactive as to be regarded as perhaps the "most noble" of the noble gases. Little krypton escapes

(a) Note the reported doses here and on the previous page were in roentgens. This was before either the rep or the rad had general usage.

(b) The book by Dr. Hymer Friedell on the history of biomedical activities in the Manhattan Project, cited in chapter 9, notes exposure of rabbits as well as guinea pigs and mice as mentioned in these pages. Thus, enough was made to expose larger animals, but not for toxicology.

(c) One hundred days' operation followed by sixty days' cooling.

(d) The radioxenon was prepared by deuteron transmutation of ¹²⁷I.

from reactors in the absence of cladding failures. However, large quantities can be released during fuel reprocessing. By virtue of its lack of reactivity, it is very difficult to trap. The potential impact of its release on levels of worldwide contamination were appreciated in the later years of the war. Nevertheless, there is essentially no record that this author has been able to find of biomedical work with krypton during the MED days. Apparently work with xenon and argon gave the early workers all the cues they needed to make decisions about the radioactive noble gases. The fact was established that exchange was rapid in both directions and biological half-lives were short, except for fat.

B. Iodine Vapor

It must be remembered that iodine isotopes had been around for some time before World War II or the Manhattan Project (chapter 5). The pioneer work had already been done, much of it at Berkeley and Massachusetts Institute of Technology (MIT). It was familiar territory compared to the new fission products and the actinides. It is not surprising, therefore, that there was not a large effort devoted to iodine during the MED days, except for the new isotopes that appeared after fission and continuation of the clinical applications.

The potential hazard of inhaled ^{131}I is addressed by calculation in the Metallurgical Project monthly report dated May 1943. Experimental work by inhalation had to await the availability of ^{131}I , a considerable improvement over ^{128}I (with its twenty-five-minute half-life) used in earlier noninhalation work (see chapter 5).

Experiments involving both sufficient material and enough animals for more than spot-check-type results were done about 1944 at Chicago (Dailey, Wender, and Abrams 1945). They used a manifold arrangement similar to that shown in figure 9.5C of chapter 9.^(a)

The abstract of this document gives the high points as seen by the authors:

Radioactive ^{131}I was obtained from pile bombarded tellurium, from sump water from the extraction plant at Site X, and from fumes evolved from solution of bombarded slugs. An oxidizing agent (usually KIO_3 or $\text{H}_2\text{O}_2 - \text{FeSO}_4$) was added to a solution of radioactive iodide and iodine gas was thus evolved. The radioactive iodine gas was mixed with air and passed through a manifold from which 21 anaesthetized rats breathed. Tissues were wet-ashed for measurement of activity due to ^{131}I .

Results of two experiments indicated that about 10 percent of the inhaled I_2^{131} was retained by the rats. Of that which was retained at the end of a 30 minute exposure only five percent was in the lung and some of this was probably in pulmonary blood. Hence absorption of I_2 from the lung was practically instantaneous. The thyroid contained 10 percent of the retained iodine at 48 hours; the remaining 90 percent was excreted in the urine. The fate of iodine absorbed from the lung is similar to that of ingested iodide.

(Dailey, Wender, and Abrams 1945)

Distribution to the tissues and excretion of iodine taken in as a vapor are shown in figure 10.1, taken from the Chicago work.

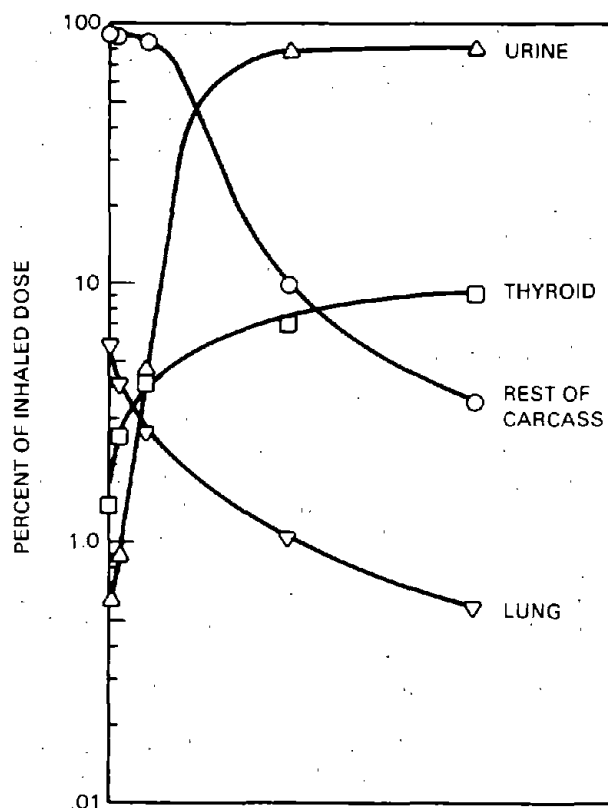
(a) Iodine vapor is a lung irritant (more effective than chlorine). As a result, relatively little experimental work had been possible by inhalation before the advent of radioisotopes of iodine. These made work with the vapor feasible by virtue of the much smaller quantities required.

FIGURE 10.1. Distribution of inhaled $^{131}\text{I}_2$ in rats. (Redrawn from Dailey, Wender, and Abrams 1945.)

At Berkeley, the iodine isotopes formed in nuclear fission were part of the large enterprise involving parenteral and ingestion routes described in chapter 6. As with other very soluble compounds, the behavior after ingestion was considered a good substitute for inhalation work. Perhaps for this reason, experiments specific to iodine vapor do not appear in the MED work at Berkeley.

In 1944, a good summary of the status of radioiodine in physiology and metabolism was prepared by the Berkeley group (Hamilton 1944).^(a) This is clinically oriented and concerns largely data from man. A postscript on protection of personnel around the new reactors is the suggestion for taking 100 mg of stable iodine per day to block absorption of iodine vapor by the thyroid. We have no records of this having been done.

At the very end of the MED days, quite large quantities of ^{131}I were becoming available. As part of the transition to peacetime enterprises, laboratories like Berkeley began greatly expanded programs for radioiodine in diagnosis and therapy. These do not concern inhalation problems and will be reserved for our discussion of the relationships between internal emitter toxicology and nuclear medicine.



C. Other Respirable Gases

While the presence of tritium and tritiated water vapor and of ^{14}C as radioactive carbon dioxide was recognized in the mixed fission and activation products, their amounts and potential toxicity were considered of minor importance in

(a) This report was classified "Secret" even though it was made up entirely of quotations from open literature publications. Nothing could get out that gave any hint that radiation problems might play a part in the interests of the Manhattan District, a fact that accounts for many apparently stupid procedures.

relation to the cadre of new radionuclides requiring study in the Manhattan Project laboratories. Essentially no work on the toxicology of tritium, etc. was done during the MED days.

III. Postwar Work with the Noble Gases and Iodine Vapor

A. The Noble Gases, Especially Krypton and Xenon

1. Computational Approaches

In contrast to the relative paucity of biomedical investigations on krypton in the MED work, a considerable effort was mounted in the early postwar years. Plans for a nuclear power industry of considerable magnitude and anticipated fuel reprocessing activities, both civilian and military, focused attention on the krypton (mostly ^{85}Kr) that might be released. Work on xenon isotopes continued.

By this time, the potential for chemical reactions of the noble gases with fluorine, oxygen, etc., had been discovered along with the quasi-physical process of clathrate formation.^(a) Xenon, the most reactive of the noble gases, was postulated to produce clathrate-type side chains with body proteins—a possible explanation for its narcotic effects.

Projections of the accumulation of radioactive gases in the atmosphere were made by many laboratories and cognizant agencies of government. Acid treatment of fuel elements releases many substances in gaseous form. Krypton-85 and tritium are released in sufficient quantity and possess long enough half-lives (10.76 and 12.26 yr, respectively) to accumulate to a considerable degree if releases are not controlled. For example, about 5,000 Ci of ^{85}Kr may be released per batch of spent fuel processed at an installation such as the Nuclear Fuel Services operation at West Valley, New York.^(b)

Thus, the total accumulation could be in the megacurie range. Indeed, Whipple (1969) estimated that ^{85}Kr emission might limit U.S. nuclear power activities to about 150,000 megawatts of electrical energy (MWe).

Radioactive krypton and xenon are also produced in nuclear explosions. One source (Unruh 1970a,b) calculates 5×10^4 Ci of ^{85}Kr have been produced by nuclear explosives. This is small compared to the 1,300 Ci per day per 1,000 MWe from reprocessing of fuels from nuclear power plants. Estimates of total free-world production of ^{85}Kr varied considerably (Kirk 1972) even in the 1960s and early 1970s. With the failure of nuclear power to develop as anticipated, most projections are probably now too high. Yet, we find it useful to quote some round numbers: by 1980, about 200 megacuries; by 1990, about 1,000 megacuries; by 2000, about 3,500 megacuries.

Figures for other noble gases are lower because of shorter half-lives (e.g., ^{133}Xe , 5.2 days) or lower fission yield.

(a) A clathrate is a solid that incorporates a gas into voids in its crystal structure. Both water (hydrates) and organic solvents exhibit such behavior. Kirk (1972) pictures the structure of a hydroquinone clathrate.

(b) This facility is not in operation now. Neither has the nuclear industry grown according to early projections. Nevertheless, the calculations are informative.

What biological significance do these apparently enormous amounts have, especially as an inhalation hazard? Still using the computational approach, we recognize the enormous dilution accomplished by the earth's atmosphere. Hendrickson at Battelle (1970) estimated, using data from several sources, that the concentration represented by total inventories toward the top of the global estimates would be on the order of $3 \times 10^{-7} \mu\text{Ci}/\text{cm}^3$. This is one-tenth of the then-existing maximum permissible concentration for continuous occupational exposure to ^{85}Kr of the International Commission on Radiological Protection (ICRP) and the National Council on Radiation Protection and Measurements (NCRP). This amount would yield annual doses to the whole-body surface of 500 mrem, to the skin of 300 mrem, and to the lung of about 12 mrem. The dose to lung on inhalation was calculated by Whitton (1968) of the United Kingdom at about 5 mrem from ^{85}Kr in the lung and 7 mrem from external radiation.

These and other calculations have resulted in the conclusion that the doses to the lung from noble gases in the environment are small in comparison to those associated with the external radiation from immersion in a passing cloud of the gases. Skin becomes the critical organ for ^{85}Kr for example. Doses could be 0.5 rem per year at the skin surface, 0.3 rem per year in the shallowest layer of live skin; to be compared to 0.005 rem to the internal surface of the lung and 4×10^{-7} rem per year to the lens of the eye—all from continuous immersion in air with a concentration of $3 \times 10^{-7} \text{ Ci}/\text{cm}^3$ of ^{85}Kr (Hendrickson 1970).

The idea that the submersion dose is controlling has taken over for all of the noble gases except, of course, radon, which presents an entirely different problem. Officially it is an "infinite hemispheric cloud." Walter Snyder, of Oak Ridge National Laboratory, the dean of the calculators for internal emitter standards, produced several papers with his colleagues, just before his untimely death, on the doses from various scenarios of immersion in clouds of released gases. An example is Bernard and Snyder (1975), which concerns dose on inhalation of noble gases.

What of the noble gases dissolved in body fat? Using ^{85}Kr again as an example, we find that calculated internal dose in the fat can indeed be over two orders of magnitude higher than the lung dose from the beta-particle component (the gamma component is much lower). Fat is, of course, a very radioresistant component of tissues. But the external dose is yet another order of magnitude higher than the dose even to fat (Diethorn and Stockho 1972). Hence, the importance of immersion over inhalation persists even if the high solubility in fat depots is considered. The primary effect of the fat is to slow release of residual amounts after the easily diffusible portions have left the body.

The noble gases have been used for many years in numerous procedures in medicine (see, for example, Bennett et al. 1965; Wagner 1965). Most of these are diagnostic and concern respiratory or circulatory functions or determination of total body fat. In these cases, the gas may be given in radioactive form for ease of measurement and is, of course, inhaled. No immersion dose is involved. Lassen (1964) from Copenhagen has assessed tissue radiation doses from two noble gases, krypton and xenon, as well as tritium given in this manner. Tracheal mucosa received up to 96% of the total dose; lung up to 17%; adipose tissue between 8% and 9% depending on body build; gonads around 1%; and other tissues between 1% and 2% of the dose from ^{133}Xe inhalation. Corresponding figures for ^{85}Kr inhalation were higher for lung but lower for all other tissues, including tracheal mucosa.

These calculations do not mean any real change in the evaluation of hazard from noble gases. As calculated by Lassen (1964), the actual doses are still at a maximum of about 100 mrad from inhalation of a concentration of $1 \mu\text{Ci}/\text{ml}$ for one minute, which is equivalent to an injection of 5 mCi of the isotope.

The general result of all the calculations can be summarized in the broad generalization that inhalation of millicurie amounts of the common radioactive noble gases results in millirad doses. This stands in stark contrast to the phenomena we saw in chapter 9.

2. Experimental Approaches

The experimental work concerns largely the tissue mobility of noble gases, seen amply in the various clinical applications in nuclear medicine, better determination of partition coefficients in tissues, and a small amount of work on effects.

Experimental programs on krypton began almost simultaneously, one by Kirk and Morken started at Rochester and continued at the Environmental Protection Agency (EPA) Regional Laboratory in Montgomery, Alabama (Kirk);^(a) another at Hanford in work by Ballou, Willard, and colleagues; and a third at Brookhaven on the kinetics of inhaled krypton in man (Ellis et al. 1977). It is not clear why the midseventies should have nurtured these fairly substantial efforts after years of relative inactivity. The *raison d'être* given by Ballou (1976) is the continuing expansion of the nuclear industry and the fact that most hazard estimates for elemental tritium^(b) and ^{85}Kr were based on dose calculations derived largely from physical rather than biological data. Kirk got into the field for some of the same reasons, but, in addition, krypton made a good thesis study area and his supporting agency apparently encouraged him to study the noble gases. It is likely that interest was expressed at the Atomic Energy Commission (AEC) in having more work on krypton. Kirk and Morken, publishing from North Carolina and Rochester, respectively, studied the saturation and desaturation kinetics for ^{85}Kr in guinea pigs breathing a krypton-air mixture (Kirk and Morken 1975 and earlier work quoted therein). There were usually four components to the curves with half-times ranging from less than 2 min to between 88 and 178 min. Association with various conceptualized compartments was reasonably good, except that the half-times were longer than predicted.

A glimpse of the distribution of krypton in man at from 0.45 to 27.85 hr after administration is shown in figure 10.2. This information was obtained by whole-body-counting techniques.

A discouraging aspect of all of this work, and the results of a thorough review of the literature, was the variability of the rates. They varied not only among individual animals of a given species but in the same animal at different times. However, it was apparent that the average times required for saturation and

(a) William P. Kirk, a Public Health Service officer, was assigned to the University of Rochester for Ph.D. studies in the early postwar years. He produced a Ph.D. thesis on krypton effects working with Donald A. Morken, whom we met in the radon chapter. The review cited was produced from Southeastern Environmental Radiation Laboratory of the then Bureau of Radiological Health at Montgomery, Alabama, where Kirk continued experimental work in the field for many years. The review was based in part on his Ph.D. thesis. In the 1970s, Kirk moved to the Experimental Biology Laboratory of the EPA National Environmental Research Center in Research Triangle Park, North Carolina.

(b) The original announcement of the new project included tritium.

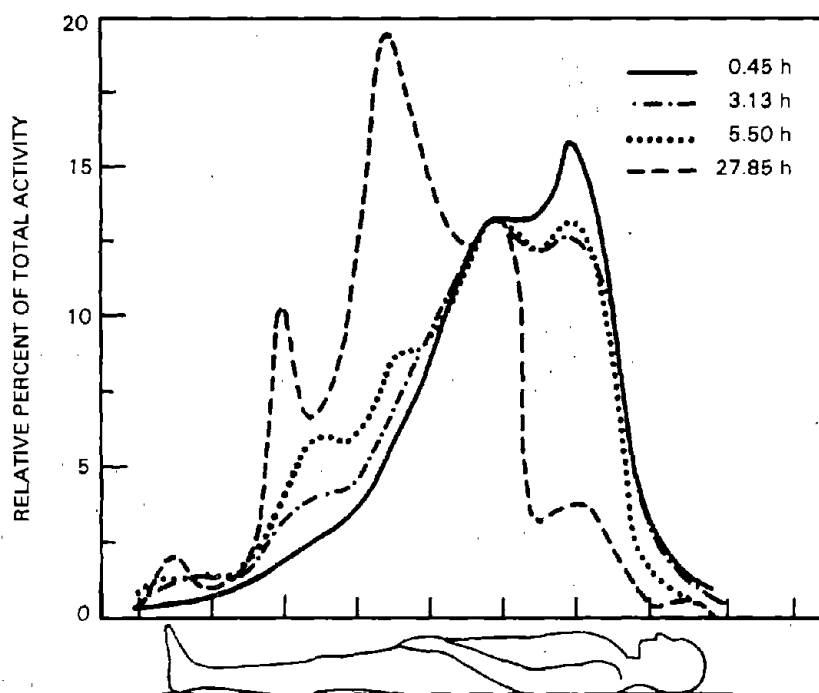


FIGURE 10.2. A typical profile distribution of ^{79}Kr in man, based on the coincidence counting mode of the whole-body counter. (Redrawn from Ellis et al. 1977. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1977.)

desaturation are related to body size, being slower, as might be expected, in larger species. This work harks back to early postwar work by Tobias et al. at Berkeley (1949), which pioneered some of the current ideas concerning the behavior of noble gases in vivo.^(a,b)

Is it possible to produce acute radiation effects with these relatively benign radioactive noble gases? Indeed it is. We should remember that even high activity concentrations do not represent much mass. Kirk, Rehnberg, and Morken (1975), publishing again from the EPA center at Research Triangle, North Carolina and the University of Rochester, conducted a thorough study of the acute lethality of ^{85}Kr . They used nose-only exposures with individual exposure chambers attached to a ventilated plenum, much as described in the previous chapter. Exposures lasted twelve hours, with periodic purging of the body chambers to prevent accumulation of krypton by leakage around the latex collars. The observation period was sixty days.

- (a) Table 1 in the Kirk publication provides a handy summary of the compartmental half-times for ^{85}Kr obtained over years of work in many laboratories.
- (b) At Rochester, Nussbaum and Hursh (1957) determined the preferential solubility of radon in body fats in the midfifties. The partition coefficients were similar to those of other noble gases.

A typical lethality curve is given as figure 10.3. The exposure is given as a time-concentration unit ($\mu\text{Ci}/\text{cm}^3$)·hr, and the median lethal exposures calculated by two methods are given in the body of the graph.

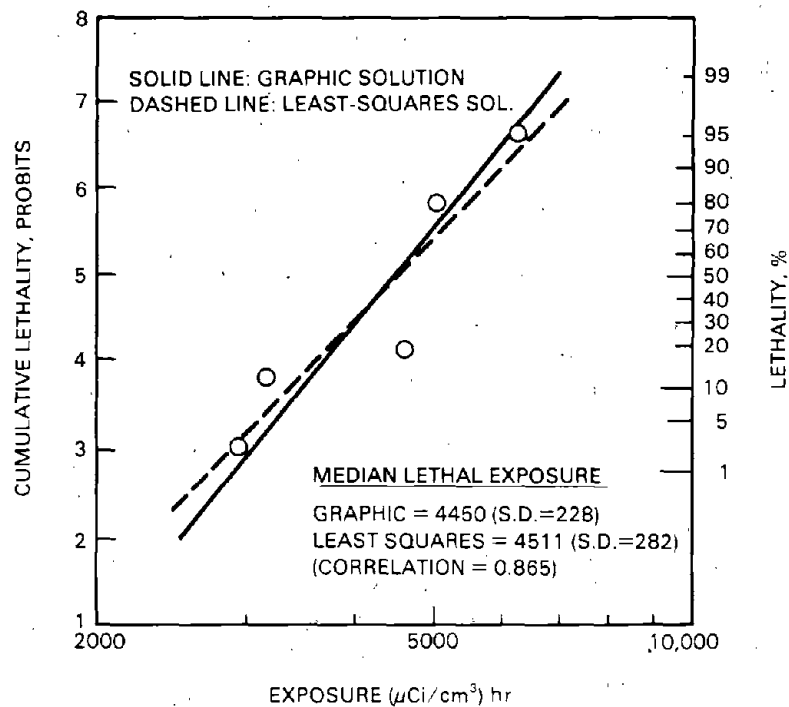


FIGURE 10.3. Lethality curve—guinea pigs exposed to ^{85}Kr via respiratory route. (Redrawn from Kirk, Rehnberg, and Morken 1975. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1975.)

Doses, shown below,^(a) were calculated from knowledge of the partition of krypton in the tissues and on the assumption that a steady state existed during exposure with saturation and desaturation kinetics being mirror images of each other.

Exposure	Estimated Beta Dose (rad)		
	Bone Marrow	Whole Body	Lungs
4450 ($\mu\text{Ci}/\text{cm}^3$)·hr. (The median lethal exposure by graphical solution)	316	340	7876
4511 ($\mu\text{Ci}/\text{cm}^3$)·hr. (The median lethal exposure by least-squares method)	320	345	7984

(a) Modified from Kirk, Rehnberg, and Morken (1975).

Clinical observations except weight loss were difficult to correlate with exposure because many were not anticipated and were not recorded consistently. All the obvious ones were related to the respiratory system or the exposed nose and eyes. Epilation and dry desquamation were reversible. Nevertheless, serial pathology and hematology information indicated serious involvement of the hematopoietic system. While lung damage was the predominant injury in animals surviving more than thirty days, it was not the sole contributor.

These results led the authors to speculate on the validity of earlier conclusions that the important dose from immersion in an infinite cloud is entirely the external dose, at least with the soft beta particles of krypton. Depending upon skin characteristics, the lung or hematopoietic system might be injured as much as the skin. They suggested a need for infinite-cloud lethality studies to settle the issue, also to establish the possibility of skin tumors from chronic exposures. Some of this was taken up in the Plowshare program, which we shall examine later.

The Hanford work with ^{85}Kr began in fiscal year 1976 and has been reported upon in every annual report since. It included accumulation and tissue distribution in adult rats, dogs, and sheep, also in gravid rats and pregnant sheep, and finally, relatively long-term toxicity to both adult and embryo. Total body exposure of newborn rats was added to simulate external exposure from cloud passage.

The work on accumulation and tissue distribution began at quite low levels, comparable to the maximum permissible air concentration. The majority of tissues equilibrated quickly. Body fat and gastrointestinal tract were slower, requiring nearly four hours to reach equilibrium. There were some surprises in the desaturation curves. Gastrointestinal tract, which was slow to saturate, lost the krypton quite rapidly. The adrenal gland, which saturated quickly, retained the krypton for several hours.

Dose calculations were made for the rat (Willard and Balliou 1977a) for chronic exposures based on the kinetics determined in the acute four-hour exposures. Surprises are that the doses to adrenals, fat, ovaries, and pelt exceeded those to lungs, with contents of the large intestine close behind. On this basis, dosimetry based on ideas of more or less uniform accumulation and retention except for fat, as might be done without these biological data, could be considerably in error. On the other hand, the actual doses accruing from exposure at the $(\text{MPC})_a$, $(a) 3 \times 10^{-7} \mu\text{Ci } ^{85}\text{Kr}/\text{m}^3$, are exceedingly small. Both of these points are illustrated in table 10.1. Skin surface doses under these same conditions would be very much higher (e.g., rad per day).

In the same annual report, Willard and Ballou (1977b) compare retention kinetics in rat and dog. They were very similar with a short-lived component (5- to 7-min half-life) accounting for 40% to 45% of the activity and a longer-lived component (40- to 60-min half-life) accounting for the balance.

Later work (Willard et al. 1978) suggested three components for whole-body clearance in the dog (5-, 30-, and 100-min half-lives) and calculated radiation doses were in somewhat different order, although still quite low. These put lung at the top and adrenals fifth, but this is artificial since the lungs were full of the ^{85}Kr atmosphere at the time of sacrifice. The partition coefficients and calculated dose for chronic exposure are shown in table 10.2.

(a) $(\text{MPC})_a$ Maximum permissible concentration in air.

TABLE 10.1. Partition Coefficients and Dose Estimates for Rats Exposed to ^{85}Kr Atmospheres

	Number of Rats	Partition Coefficient +SD	Dose at MPCa (Unrestricted) ($\mu\text{rad}/\text{year}$)
Adrenals	12	0.372 ± 0.269	467
Fat	17	0.346 ± 0.046	434
Ovaries	4	0.176 ± 0.078	221
Pelt	17	0.154 ± 0.034	193
Lungs	15	0.074 ± 0.027	93
Testis	8	0.050 ± 0.007	62
Muscle	11	0.046 ± 0.016	58
Kidneys	13	0.042 ± 0.008	58
Spleen	11	0.034 ± 0.009	43
Liver	15	0.022 ± 0.004	28
Bone	11	0.015 ± 0.004	19
Heart	13	0.012 ± 0.007	15
Brain	12	0.007 ± 0.002	9
Large Intestine Contents	12	0.138 ± 0.032	173
Jejunum Contents	12	0.085 ± 0.068	107
Large Intestine	17	0.081 ± 0.042	102
Cecum	15	0.058 ± 0.033	73
Stomach Contents	12	0.054 ± 0.018	68
Ileum	17	0.050 ± 0.023	63
Ileum Contents	12	0.050 ± 0.030	63
Jejunum	17	0.047 ± 0.014	59
Stomach	15	0.038 ± 0.009	48
Duodenum	17	0.036 ± 0.031	45
Duodenum Contents	10	0.030 ± 0.015	38
Cecum Contents	12	0.028 ± 0.017	35

Source: Reset from Willard and Ballou 1977a.

TABLE 10.2. Partition Coefficients and Radiation Dose for ^{85}Kr in Dog Tissues(a)

Tissue	Partition Coefficient $\mu\text{Ci}/\text{g}/\mu\text{Ci}/\text{ml}$	Tissue Dose for Chronic Exposure to MPCa, $\mu\text{rad}/\text{yr}$
Lung	0.477	599
Bone Marrow	0.254	319
Fat	0.205	258
Jejunum Content	0.137	173
Adrenals	0.130	163
Lymph Nodes	0.108	136
Ileum Content	0.094	118
Pelt	0.082	103
Pancreas	0.065	82
Thyroid	0.064	80
(a) Average of 6 dogs.		

Source: Reset from Willard et al. 1978.

The accumulation and deposition of ^{85}Kr in pregnant animals indicated the same general behavior as in adults (Andrew, Sikov, and Willard 1977) except that, in general, the fetal tissue contents were lower than those of the adult (e.g., in sheep, see Andrew et al. 1978, figure 3.42). This was especially true of fetal versus adult fat. The authors do not speculate on what this might indicate regarding placental transfer of a noble gas like krypton.

The Hanford group, having established the pharmacokinetics to their satisfaction, turned to much higher exposure levels in order to determine effects. Again they looked at adults, newborn, and embryos. The most extensive experiment was chronic exposure of rats to air concentrations of 3×10^{-3} , 3×10^{-4} , and $3 \times 10^{-5} \mu\text{Ci}/\text{ml}$ for their life span. These are to be compared to the $(\text{MPC})_a$ of $3 \times 10^{-7} \mu\text{Ci}/\text{ml}$. The exposures started in June 1978. The highest air concentration yielded cumulative radiation doses for the first year of 2,000 rad to the skin, 22 rad to the lung from both the krypton incorporated in lung tissue and that in the airways, 5.2 rad to adrenals, 4.8 rad to fat, and less than 1 rad to all other tissues (Willard et al. 1979). This was reported on further in 1980, 1981, and 1982. Exposures were terminated for budgetary reasons at 808 days, but effects on survival were already well established by this time. The remaining animals were kept for life-span study.

Survival of the exposed groups was not significantly different from controls except for one anomaly, the middle-dose group. Malignant lesions were not significantly higher in any of the exposed groups, even skin tumors. Leukemia incidence was not notably different either (Willard, Tolley, and Ballou 1981; Ballou 1982). Ballou concluded that these results "attest the conservatism of the established limits for occupational and population exposure to ^{85}Kr " (Ballou 1982).

When newborn animals were exposed to concentrations producing skin doses of 850, 2,300, and 4,700 rad (Ballou and DeFord 1981), there were from 44% to 100% skin lesions and mortality from 33% to 80%. Follow-through on histopathology showed that newborn rats (two studies) developed skin carcinomas and leukemia after exposures at approximately 5.2, 12.7, and $25.9 \mu\text{Ci}/\text{ml}$ for six hours (Ballou 1982). The carcinoma incidence was dose related. The leukemias were too few to attempt dose-response correlations. The skin dose was approximately 958, 2,328, and 4,738 rad, respectively, at the three dosage levels.

By lack of mention, we must assume that skin lesions were not seen in the work at 10^2 , 10^3 , and 10^4 times the $(\text{MPC})_a$, just as life-span shortening and malignant tumors were not seen. The results thus tell us that (1) we are correct in considering skin the critical organ for ^{85}Kr exposure, and (2) the radiation doses from these noble gases required to produce lesions are at least as high, if not higher, than those associated with similar effects from x- or gamma-radiation.

The work at Brookhaven was done in the medical department and used sixteen human subjects (Susskind et al. 1977; Ellis et al. 1977). They inhaled a ^{79}Kr -air mixture from a spirometer system for about 10 min during which the concentration of ^{79}Kr was monitored by a detector at the mouthpiece and in the chest region by a wide-field gamma camera. After 10 min, the system was switched to room air, and the ^{79}Kr activity of the expired air and of the chest region was monitored continuously. This was called the "washout phase" and showed rapid clearance with half-times in two phases—a very rapid one of about 20 sec and a second one of about 4.7 min half-time. There was variability in these, especially the second phase, but it was not as large as mentioned in the Kirk-Morken work (standard deviation of ± 2.05 for the 4.74-min half-life).

After the initial "washout phase," the subjects went to the Brookhaven whole-body counter for a series of measurements extending out to as long as 55 hr. The characteristics of the Brookhaven counter allowed measurements out to quite low counts. There were at least three half-times that could be associated with this later period. The mean half-lives were 0.33, 2.41, and about 7 hr. A profile of the distribution in various parts of the body as a function of time could be drawn by putting the counter in a coincidence counting mode. This was seen in figure 10.2.

The half-time of the long-term component correlated highly with the percentage of total body fat and with half-times in the literature for adipose tissue. The profile (figure 10.2) also shows localization and longer retention in body regions of high fat content (upper thighs and lower abdomen). While the authors do not comment on the point, it would seem that this system would be useful in clinical measurements. By virtue of this work, the kinetics of krypton are well established in man.

Before we leave the noble gases, we should pause momentarily to recognize, as did Kirk (1972), that there are still unexplained phenomena regarding the biological effects of these elements. Most of them occur at high pressures. However, some, such as inhalation anesthesia in man, inhibition of the growth of fungi, etc., occur at partial pressures and total pressures consistent with normal physiological function (Buchheit, Schreiner, and Doeblner 1966). There have even been reports of radioprotection, as well as potentiation, with xenon and krypton (Markoe, Anigstein, and Schulz 1970).

On the whole, the experimental work has done little to controvert the conclusions drawn from the computational approach, but such was not expected. It has supported the general view that these elements present hazards of quite a different nature from the inhaled particles (Cohn, Ellis, and Susskind 1979). That this does not extend to all of the mobile gases we will see in subsequent sections.

B. Iodine Vapor

1. The Setting

The several isotopes of iodine are among the most abundant of the fission products. We have already noted that iodine was among the earliest of the radioactive materials to be discovered in the environs of the Hanford reactors and fuel processing plants. This was responsible for the large program with sheep that we reviewed in chapter 8. Ingestion was the route of administration chosen for that work since the principal problem appeared to be deposition of iodine vapor and salts therefrom on vegetation. This decision is probably correct for releases from routine operations, since the air concentrations would ordinarily not be high enough to present an inhalation hazard that was greater than the hazard from ingestion of accumulated depositions.

In the case of larger releases under accident situations, the air concentrations of the radioiodines might be quite high. Whether inhalation is or is not the controlling route of entry depends upon conditions.

For many years, health physicists, meteorologists, environmentalists, and regulators have sought to quantify the behavior of airborne effluents from reactor and fuel processing operations. Modeling was the predominant approach, although there were occasional field checks with known and controlled releases (chapter 14). Iodine releases occupy a prominent place in all such modeling.

The reader is referred to the three-volume proceedings of a Health Physics Society midyear topical symposium on reactor siting held at Idaho Falls, Idaho, in November 1970 (HPS 1971); also to an international symposium on fission product release and transport held at Oak Ridge in 1965 (ORNL 1965); and to the Air Cleaning Conferences and the Conferences on the Peaceful Uses of Atomic Energy referenced in chapter 9. These in turn were greatly expanded in the 1970s by the Reactor Hazard Evaluation Study ("Rasmussen Report," NRC 1975) and a host of environmental impact statements. We will have occasion to look at some of these in later chapters. For our present purposes, it is sufficient to review first the modeling approach and then the experimental data applicable to iodine vapor releases.

The widespread uses of iodine and iodinated compounds in clinical medicine has generated a tremendous literature. A sizeable portion concerns untoward, i.e., toxic, effects. However, iodine vapor is almost never considered to be the culprit in these situations. We will review these aspects when we consider the relationship of internal emitter toxicology to nuclear medicine in chapter 20.

2. Reactor and Related Hazards

There is no question that most of the iodine inventory in a power reactor would be in vapor form at the temperatures in the core and in the fuel rods; this is even more true in a serious loss-of-coolant accident (LOCA). However, the events subsequent to release can be quite variable.

First we should consider the cadre of iodine isotopes likely to be present in an operating reactor; most of them are depicted in table 10.3.

TABLE 10.3: Selected Iodine Isotopes

Mass Number	Half-Life	Direct Fission Yield, Percent	Yield from Fission Product Chains, Percent	E _{max} (β), MeV
123	13.3 hr			E.C. 0.16
125	60.2 da			E.C. 0.035
127	Stable	0.0	0.1	Stable
128	25 min	—	—	2.12
129	1.6 x 10 ⁷ yr	0.0	0.8	0.15
130	12.5 hr			1.02
131	8.05 da	0.0	2.9	0.61
132	2.3 hr	0.2	4.4	2.1
133	21 hr	0.6	6.6	1.27
134	52.5 min	2.2	7.8	2.5
135	6.7 hr	2.9	5.5	1.4
136	86 sec	2.9	3.9	5.6
137	22 sec	2.2	2.7	*
138	5.9 sec	1.3	1.5	—
139	2.7 sec	0.8	0.8	*
140	1.5 sec	0.3	0.3	—

* daughter radiations from xenon isotopes.

E.C. = Electron Capture.

Source: Modified from Holland 1963. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1963.

Quite obviously, only the isotopes 131 through 135 ^(a) are of importance as potential inhalation hazards. The earlier members have half-lives that are too long; the later members have half-lives that are too short. Quite obviously also, the decay rates of 132 through 135 leaves only 131 as a possible isotope to be reckoned with if there has been appreciable "cooling" of the reactor fuel before release of the iodine in, for example, fuel reprocessing or waste disposal. If the delay has been considerable, even 131 would be unimportant.

Lest we be lulled into complacency by the predominance of short half-lives among the iodine isotopes, we should recognize the enormous inventory of the iodines in a reactor core at "saturation," i.e., when equilibrium of generation and decay is reached. This is shown in table 10.4, taken from NCRP 1977. (These figures are comparable to the inventory calculated in the voluminous Reactor Safety Study begun by AEC and issued by the then-new Nuclear Regulatory Commission [NRC 1975].)

TABLE 10.4. Saturation Inventory of Iodine Isotopes in a Reactor Core^{a,b}

Isotope	Activity
	(Ci/MWt ^c) $\times 10^4$
131	2.5
132	3.8
133	5.6
134	6.6
135	5.1

^aFor the calculation of saturation activities see Appendix A.

^bThe values for the saturation inventory shown in this table are essentially the same as those calculated for the "Reactor Safety Study," WASH-1400 (NRC 1975), which appeared during the preparation of the final draft of the present report. The calculation of the values in the table involves ^{235}U thermal fission yields at constant power for three years with removal of radionuclides only by radioactive decay. The calculation of the values for the WASH-1400 report involves the ORIGEN code which is more realistic (including neutron absorption, three-region core, loss by neutron capture, Pu buildup, etc.). Since the maximum difference between the two results is <12 percent of these iodine nuclides, the values in this table are retained because these have been used to obtain the results on absorbed dose which appear in Appendix B. The results in Appendix B have been prepared especially for this report since no documentable reference is available in the literature.

^cMWt is megawatts thermal.

Source: NCRP 1977. Reprinted with permission of the National Council on Radiation Protection and Measurements, Bethesda, Maryland, copyright 1977.

Even with materials of short half-life, this enormous inventory is sufficient to supply ample iodine vapor to pose inhalation and/or ingestion hazards in the event of a serious reactor accident (e.g., LOCA). Even lesser accidents and ones of a different type, such as the releases at the Windscale reactor in England in 1957, can be significant. It is estimated that 20,000 Ci of ^{131}I were released to the environment from this air-cooled and uncontained reactor (chapter 11).

(a) The long-lived 129 isotope will contribute significantly to the iodine content of the biosphere and cannot be neglected. However, it is most unlikely to be an inhalation hazard.

3. How Important is the Inhalation of Iodine Vapor?

As part of the first National Academy of Sciences National Research Council (NAS-NRC) review of fallout problems (the BEAR reports, i.e., Biological Effects of Atomic Radiation), much attention was directed to the thyroid. When the Federal Radiation Council (FRC) was organized (see chapter 16), it requested opinions from the NAS-NRC on pathological effects of thyroid irradiation. The report (FRC 1962) was focused on fallout from weapons testing and dismissed the absorption of ^{131}I by inhalation as unimportant "except possibly in fall-out intensities which are intolerable for other reasons" (p. 2).^(a) The food chain, especially milk, seemed the most important route. This was reiterated by Wehmann (1963) at Idaho Falls using the results of field releases of iodine and calculations therefrom.

The Rasmussen study of reactor safety (NRC 1975) concludes that the escape fraction of elemental iodine from reactor core material would be very large. It considers the reactivity of iodine vapor with many substances and the consequent production of iodides of different volatilities, including hydriodic acid. The study postulates that escape of from 50% to 100% of the iodine inventory can be expected with either a meltdown or "gap release." They took 90% as the probable value. Considering the size of the inventory, an acute inhalation hazard could easily exist were any large fraction to be released to the environment, whether it be 50%, 90%, or 100%. Thus, again the dismissal of inhaled iodine in the FRC report is found not to be universally correct.

The NCRP report already cited uses two models, a conservative and a realistic one. It calculates noble gas and iodine fractions available for release in a LOCA. They are estimated for both boiling water reactors (BWR) and pressurized water reactors (PWR). The iodine release fraction from the PWR is 25% on the conservative model, only 2% on the realistic model. For the BWR, equivalent figures are 25% and 0.04%. (It is not clear why these are so much lower than the releases calculated in the Rasmussen Report.) These fractions can be reduced considerably more by the presence of alkali sprays, filters, and other ways of entrapping iodine releases commonly installed in reactor containment buildings.

Absorbed doses to thyroid from ^{131}I – ^{135}I are calculated by the NCRP Committee for a variety of times after release and distances from the point of release. Maxima are 350 rad at the nearest point (0.5 mi) and longest time (720 hr after release) for the PWR and 1,700 rad for the BWR, both using the conservative model; 1,100 mrad for the PWR and 29 mrad for the BWR using the realistic model. Doses to other tissues are not mentioned because of the extraordinary ability of the thyroid to concentrate iodine and thus to receive most of the radiation dose. These calculations are for the *inhalation* route. Assumptions are made regarding breathing rates and the so-called " χ/Q " values (the concentration at a point of interest in Ci/m^3 relative to the release rate at the source in Ci/s). Thus, even though thyroid and not lung is the critical organ, the inhalation route can be the more important one in case of a large and relatively sudden release. The calculated absorbed dose due to external radiation from the cloud (plume) is from one to two orders of magnitude lower than the dose to thyroid. The importance of the external dose was thus found to be much less than in the case of the noble gases. The dose by ingestion was lower but would grow with time if contaminated food or water were consumed.

(a) The studies of the Marshallese (chapter 12) do not confirm this (Cohn 1982, personal interview).

Book (1980) has calculated thyroid doses as a function of age in the population and the mode of exposure, i.e., inhalation versus ingestion. He concludes that fetuses would receive the highest thyroid dose from radioisotopes of iodine inhaled by their mothers. Infants would receive the highest thyroid dose from radioiodines in milk. Under conditions of constant (and low) atmospheric concentrations, he calculates that the dose from milk would exceed that from inhalation. However, under conditions of a reactor accident, the dose from inhalation would be sizeable. The fetal thyroid dose from maternal inhalation is calculated as about ten times the dose to the adult thyroid.

The answer to our original question is thus, like so many scientific questions, "yes" and "no" depending on conditions of exposure, the release rate, the age of the recipient, etc. On balance, it must be concluded that inhalation of the iodines must be reckoned with, and relevant biomedical data must be at hand. Especially it must be remembered that the chemistry of iodine is quite complex, and production of volatile compounds may take place under situations where the iodine was considered to be "fixed." This may apply as much to laboratory and hospital situations as around nuclear facilities.^(a)

4. Names and Places

Before we visit the laboratories to review the experimental work on iodine vapor and closely related subjects, we should identify some of the people and their home institutions^(b) who were most involved in the dosimetric and other calculations we have just discussed:

FRC report, 1962

Chairman - S. Warren, Harvard and AEC Headquarters

Members:

H. L. Andrews - Public Health Service - National Institutes of Health

H. A. Blair - Rochester

V. P. Bond - Brookhaven

A. M. Brues - Argonne National Laboratory

R. H. Chamberlain - University of Pennsylvania

E. P. Cronkite - Brookhaven

C. E. Dunlap - Louisiana State University

J. Furth - Syracuse University

L. H. Hempelmann - Rochester

H. A. Kornberg - Hanford

S. C. Madden - University of California, Los Angeles

A. Raventos - New York University

L. Van Middlesworth - University of California, Berkeley

T. Winship - Washington Hospital Center, Washington, D.C.

NRC (Rasmussen Report), 1975

Fission Product Source Term Task Group (one of many task groups contributing to this enormous report)

Members:

M. H. Fontana - Oak Ridge National Laboratory

(a) Anomalies in the behavior of iodine, i.e., lower than expected amounts in relation to noble gases appeared in the Three Mile Island reactor mishap and have led to further examination of models.

(b) At the time of their service.

D. L. Morrison - Battelle-Columbus
 P. C. Owczarski - Battelle-Northwest
 G. W. Parker - Oak Ridge National Laboratory
 A. K. Postna - Battelle-Northwest
 R. L. Ritzmann - Battelle-Columbus
 W. A. Yuill - Aerojet-Nuclear

NCRP Report No. 55, 1977

Chairman - E. L. Saenger, University of Cincinnati

Members:

M. Eisenbud - New York University
 R. E. Goldsmith - Cincinnati
 H. S. Ingraham - New York State Department of Health
 J. B. Stanbury - Massachusetts Institute of Technology
 J. Wolff - National Institutes of Health

UC Davis Report, 1980

S. A. Book, University of California at Davis

5. Experimental Work with Iodine Vapor

The first major postwar symposium on biomedical work with iodine was held at Brookhaven National Laboratory in 1948. It did not have a single paper on iodine vapor (BNL 1948). They all concerned its use as a tracer or therapeutic agent, work that had gone on apace even during the war years. A second major, but less clinical, symposium was the second Hanford biology symposium held in 1962 (Bustad 1963). H. D. Bruner's introduction (Bruner 1963) to the proceedings tells the story of Hanford's very early concern with airborne iodine and the comprehensive and outstanding research program that grew out of it (chapter 8). Here the concerns lean heavily toward the problems of fallout and the release of iodine from nuclear facilities. Despite many reports concerning entry of iodine into biological systems and man's food, only two address the inhalation of iodine vapor directly. A third uses other routes as a surrogate for inhalation in sheep. The shift in emphasis among those concerned with internal emitter toxicology is very evident nevertheless.^(a)

In chapter 9, section IV A, work of Willard and Bair in 1958 was cited in which the behavior of iodine vapor and silver iodide particles was compared. In contrast to expectations of rapid lung clearance for the vapor and slow clearance for the insoluble iodide, it turned out that both cleared at about the same rate. Deposition favored the vapor by 70% versus 12%. This work started the realization that biological behavior on inhalation and solubility in water may bear little relation to each other. While the tissue distributions were different (figure 9.14), the results suggested that the "vapor" behaved more like a particle than was expected, and the particles behaved more like a vapor than expected. From this we can draw one of the first lessons to be gained from the experimental work—many of the situations for the respirable gases will be neither purely like the noble gases nor entirely like the inhalation of particles. In the instance of iodine, its high reactivity might quickly change the vapor state to a particulate state on inhalation.

(a) Many of the people concerned with the clinical aspects took part as well in this work.

At the 1963 Hanford symposium, Bair et al. (1963) followed up on the earlier work with inhaled iodine with a study aimed directly at the problems of releases from nuclear facilities and the idea of blocking uptake of radioiodine by stable iodine.^(a) They measured the effects of varying amounts of stable iodine (^{127}I) on the behavior of inhaled ^{131}I . Vapor of stable iodine was released from a separate generator located in a separate compartment of the usual apparatus and mixed with the radioiodine. However, it soon became evident that relatively large quantities of stable iodine would be required, and the method was not able to handle the amounts needed. Instead, a chemical generator was developed to release stable iodine and radioiodine together from a solution of sodium iodide. Less than 1% of the released iodine was associated with particles.

Both rats and dogs were used in the study, the dogs being exposed by the nose-only system to which they had been trained. Several hundred rats and four trained dogs were utilized. The amounts of ^{127}I ranged from 0 to 5,300 $\mu\text{g}/\text{l}$ in the inhaled air. The exposure concentrations of ^{131}I ranged from about 0.1 to about 6.5 $\mu\text{Ci}/\text{l}$. There was also an experiment that utilized a low iodine diet and one in which 100 mg of potassium iodine were given subcutaneously. The exposure concentrations for the dogs were lower (0.018 to 0.37 $\mu\text{Ci}/\text{l}$).

Full balance studies were done on tissues and excreta. As expected from the experience with iodine in clinical medicine, the primary route of excretion was urinary, and the rate was quite high. The results showed clearly that ^{131}I deposition in the thyroid could be much depressed by suitable additions of ^{127}I . Three graphs taken from the work with rats are given as figure 10.4A, B, and C. The first graph shows the uptake as a function of time. The second graph shows thyroid ^{131}I at forty hours as a function of the ratio $^{127}\text{I}/^{131}\text{I}$ in the inhaled air. A third graph (figure 10.4C) is a composite showing deposition of both isotopes in both rats and dogs.

The dilution of radioiodine vapor with stable iodine produced much less reduction in ^{131}I deposition in the dog than in the rat. It took up to 50 mg of stable iodine to reduce radioiodine deposition to one-half (an exposure concentration of 4.2 mg/l). The minimum lethal concentration of stable iodine is given as 14 to 18 mg/l. Hence, the maximal amount is uncomfortably close to the toxic dose. Obvious respiratory-tract irritation occurred at the higher levels, even in the rats. This impelled the use of subcutaneous injection for the highest doses of stable iodine.

This work, along with work using other routes of entry, helped to prove beyond doubt that stable iodine could greatly reduce uptake of radioiodine by the thyroid. Ideas have been bruited about of finding ways to add stable iodine to the off-gases in case of accidental discharges from nuclear facilities. However, the relative ineffectiveness seen in the dog and the large amounts needed discouraged this approach. Those concerned with planning turned to the idea of giving the stable iodine by mouth.

The NCRP report already cited (NCRP 1977) is directed primarily at the feasibility of having stocks of stable iodine both in the plants and in the near-to-site

(a) Many proposals had already been considered for adding stable iodine to dilute out the radioiodine as deposited in the thyroid. Most of these involve administration of stable iodine to the recipient and will be reviewed in chapter 19. A novel idea put forward by AEC Commissioner Wilson (Robert E. Wilson) was to have a large amount of stable iodine placed in the reactor itself in such a way that it would dilute the radioiodine in the gas stream in the event of an unplanned release.

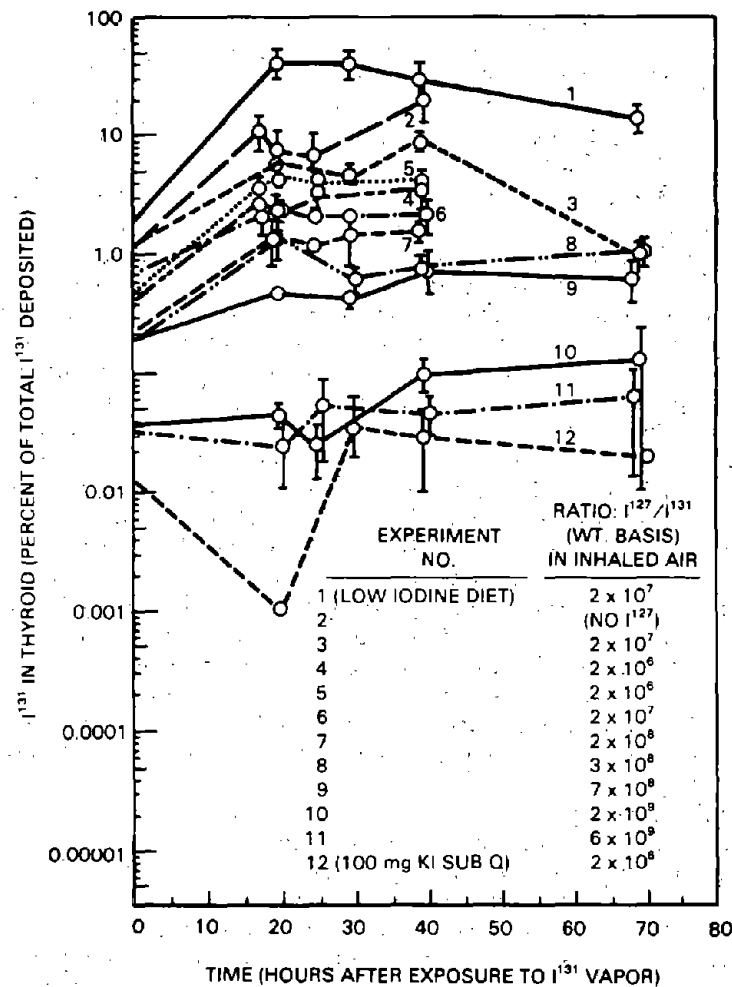


FIGURE 10.4A. Thyroid uptake of ^{131}I in rats after inhalation of ^{131}I and ^{127}I . (Redrawn from Bair et al. 1963. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1963.)

environs of possible radioiodine release sources. Because of the many questions of differences among individuals as to the condition of their thyroid, their body iodine pool, potential for reactions to iodine (allergic), etc., the report stops short of making recommendations. It does describe the possibilities. It is understood that many plants do have stocks available for use on a voluntary basis and that some communities have done likewise.

The Lovelace group worked with ^{131}I given by inhalation or injection at very low, as well as more common levels. Thomas, Scott, and Chiffelle (1970) made a point to search for effects at levels ordinarily considered "tracer" levels in medical practice. The lowest infinite dose to thyroid was, however, 286 rad, which

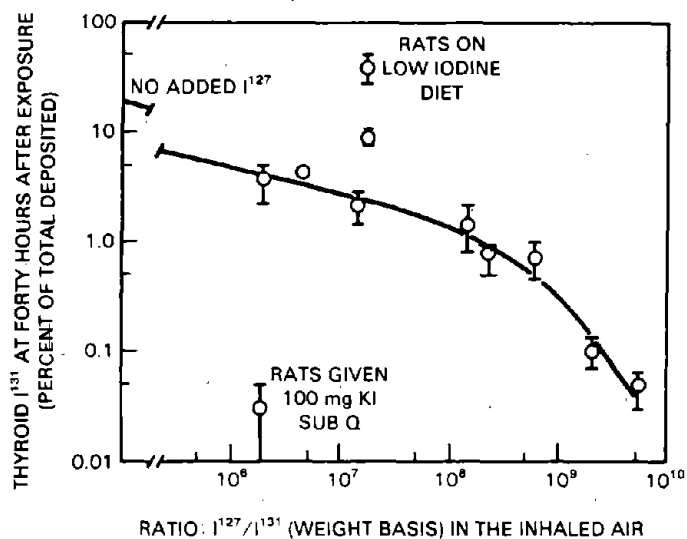


FIGURE 10.4B. Relationship of thyroid ^{131}I to $^{127}\text{I}/^{131}\text{I}$ in inhaled air. (Redrawn from Bair et al. 1963. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1963.)

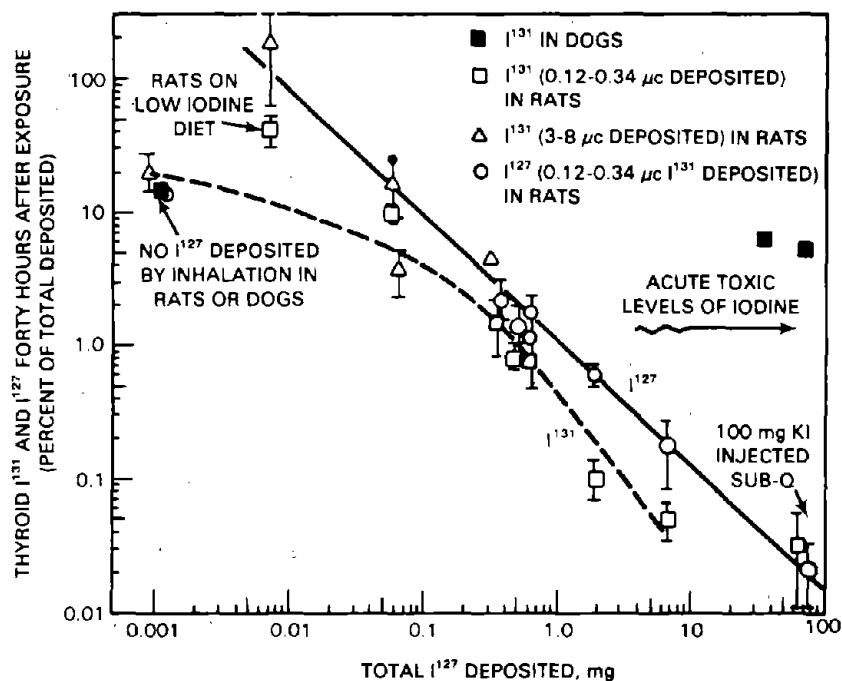


FIGURE 10.4C. Effect of ^{127}I deposition on thyroid ^{131}I and ^{127}I in rat and dog. (Redrawn from Bair et al. 1963. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1963.)

shows how difficult it is to produce a really low radiation dose to the thyroid when using radioiodine. There was some degree of biological change at all levels of dosage in this work.

There is ample evidence from the experimental work using other routes of administration that radioiodine can produce thyroid cancer, hypothyroidism, and thyroid nodules. There is no reason to expect anything different from inhaled iodine in sufficient quantity. The lowest doses in the long-term study with sheep at Hanford were low enough to be near the then maximum permissible dose rate to the thyroid. It took considerably more than this to produce thyroid tumors. We will have to assume the same relationships hold after inhalation.

Morgan, in a special editorial prepared for the 1963 Hanford iodine symposium, took a strong position on the use of the guides that had just been issued by the Federal Radiation Council. He was addressing primarily problems of fallout from nuclear tests, but the ideas apply as well to releases from nuclear facilities. He urges a strong and firm plan of action when iodine releases reach the top of Group III of the Radiation Protection Guides, viz., 10,000 μCi per day for any appreciable period. He stresses particularly the vulnerability of the young child and the fetal thyroid. Considerably lower figures would probably galvanize action today. We can conclude that there is strong contrast between toxicological importance of iodine releases as compared to the noble gases on the basis of both modeling and experimentation.

A whole new set of considerations has grown around the possible effects of certain organic compounds of iodine. Of particular interest are iodinated precursors of nucleic acids. These enter the cell nucleus and are incorporated into one of the basic components of living cells, DNA.^(a)

Similar considerations apply to compounds of tritium. We will review these in detail in connection with nuclear medicine, since that is where they have been used extensively. There is little chance of appreciable amounts of such compounds being produced after inhalation of iodine vapor.

IV. Tritium and Tritiated Water

A. Development of Interest

The existence of a radioactive isotope of hydrogen was announced in 1939 by Alvarez and Cornog (1939). It has a physical half-life of approximately 12.3 yr and decays by emission of a beta particle of very low energy ($E_{\text{max}} = 18 \text{ keV}$, $E = 5.7 \text{ keV}$) to ^3He . For convenience, it is frequently referred to by the symbol "T" rather than the more clumsy ^3H . We will use this nomenclature insofar as is convenient.^(b)

(a) Deoxyribonucleic acid.

(b) In geochemistry and some areas of environmental science, a special unit has been used to express tritium activity. This is the *Tritium Unit* (TU) or *Tritium Ratio* (TR). It was introduced by Libby and was sometimes called the Libby Unit. It represents the ratio of tritium to other hydrogen isotopes, usually in surface water. One TU is 1 tritium atom in 10^{18} atoms of the other hydrogen isotopes. This unit has not been used much in biomedical research, but it might be encountered in some of the environmental literature.

"Tritium is the most important and versatile radionuclide," (Evans 1966, 1974). If we consider its numerous tracer applications in chemistry, biochemistry, and physiology, this may well be true. In terms of radioisotope toxicology, it would have to have a lesser billing.

At room temperature, T combines with any gaseous hydrogen present to form HT. Even more readily, it supplants one hydrogen in any water vapor present to form "tritiated water," HTO, which is the most commonly encountered form of tritium in the environment. However, this reaction is far from instantaneous. Its rate depends on the presence or absence of various catalysts, the temperature, and many other factors. Fortunately, there is very ample literature in a form useful to the biomedical scientist on the reactions of tritium and tritiated water. Among these, special attention is directed to the review by Jacobs (1968) done as the first of the AEC Critical Review Series; the book by E. A. Evans of the United Kingdom Atomic Energy Authority (UKAEA) at Amersham and later the Radiochemical Centre at Amersham (Evans 1966, 1974); the first chapters of the 1979 NCRP report, *Tritium in the Environment* (NCRP 1979); the first sections of the tritium symposium sponsored by the EPA and held in Las Vegas, Nevada, in 1971 (Moghissi and Carter 1973); and the two-volume proceedings of a symposium in Vienna in 1961 sponsored by the International Atomic Energy Agency (IAEA 1962). A very useful and concise, but not easily available review, was written by Helen Woodard (1970) for the AEC's Health and Safety Laboratory.

Recently, in terms of the perspective of this book, the IAEA sponsored another symposium on tritium, this one nominally aimed at environmental problems and research (IAEA 1979). However, it provides also contemporary updating of data on man and monitoring methods. It was the result of a five-year coordinated research program sponsored by the IAEA and the Organization for Economic Cooperation and Development Nuclear Energy Agency, the U.S. Department of Energy (DOE), and Lawrence Livermore Laboratory, on behavior of tritium in various systems. The roster of papers in this volume shows very clearly the ubiquitous distribution of work on tritium both in the United States and abroad.

Willard Libby, who was for the chemistry and physical chemistry of tritium what Harold Urey was for deuterium, presented much of the early history of tritium as an introductory lecture to the EPA Las Vegas symposium (Libby 1973). He emphasized how improvements in instrumentation made it possible to detect the presence of the very low-energy beta particles from tritium. It is the presence of these very low energies that generated much of the biomedical interest, and generated also some unexpected problems as the research progressed.

In addition to the forms T, HT, and HTO, tritium is readily incorporated into organic compounds by exchange of T for H. The possible biological significance of these brought about a lively controversy. However, in this chapter we will consider T, HT, and HTO as respirable gases. The organic compounds are of less significance in this context than in tracer chemistry and nuclear medicine as they are for iodine. (Labeling of organic compounds does occur in the gas phase [IAEA 1962 Vol. II], but the reactions are slow. They require many days of constant exposure at moderately high partial pressures.)

The prewar tritium was, of course, produced by accelerators. Despite its immediate use as a tracer for studying water exchanges and pools in living organisms, there was not enough to pose a significant biological hazard. During World War II, it was recognized that tritium is produced in the fission process.

However, its great mobility and very low energy put it far behind most of the other fission products as one of the “new dimensions” we examined in chapter 6. The picture changed abruptly with the development of the hydrogen bomb and the fusion process, which requires the presence of tritium. Large quantities of tritium had to be produced, transported, and stored. It was the presence of these problems that led to the initiation of biomedical work on tritium metabolism and toxicology at Hanford—as reviewed in chapter 8.^(a) The need led to the construction of special reactors at Savannah River and a sophisticated research program.^(b) Further it was found that the fusion process produced and released much larger quantities of tritium than the fission process, and much of it was in the HT form. Consequently, much more tritium was present and releasable when the fuel was processed.^(c)

All of these increments added new dimensions in the early 1950s to tritium as a potential hazard as well as a very useful tracer and ingredient of the fusion process. We will review briefly some of the major sources of tritium and calculations of possible doses to humans, and then launch into the pertinent^(d) biomedical research at both the whole-organism and cellular level. Fortunately, there is an ample amount of such research. We will need to place less reliance on the computational approaches than we did in the case of the noble gases.

B. Source Terms and Calculations

Nearly everyone interested in tritium toxicology (as contrasted to its applications in physiology and biochemistry) has had a hand in developing estimates of the amount produced, present now, and likely to be produced. The laboratories most concerned with fallout problems and environmental impact statements have been the most active. The authors of the source-term work in the several compendia referenced in section III A present a good cross-section. So do the authors and institutions involved in the biomedical research.

We can use some rough and round numbers to illustrate tritium production rates and potential inventories, as gleaned from several sources:

- (a) A good perspective on the sudden growth of research on tritium, especially low-level releases to the environment, is given by Cohen and Higgins (1973) in the EPA tritium volume. A graph showing the number of publications on health implications of tritium and krypton shows tritium moving ahead startlingly from about 1958 on (1970 was the cutoff point). The authors discuss whether or not “the tritium problem” is all that serious. We will see here and in chapter 20 that it is the nuclear medicine aspect rather than the inhalation toxicology aspects that makes the largest difference in potential significance. Nevertheless, a very respectable literature has been developed around the toxicology of T, HT, and HTO.
- (b) Agnew (1982) very cogently points out that tritium production must continue at a rate that replaces approximately 10% of the U.S. stockpile every year simply to maintain the status quo. Unlike plutonium, tritium decays away. He points out the thirty-year age of the Savannah River reactors and their inefficiency and proposes that they should be replaced by new design systems, which could produce electric power along with the tritium. The design for such a system could be a very safe one.
- (c) Mason and Östlund (1979) from the University of Miami (Florida) estimate that the conversion of HT to HTO in the atmosphere is not rapid—“characteristic time” 6.8 yr, which, when combined with radiological decay, gives a half-time of 4.8 yr for HT in the atmosphere.
- (d) Pertinent to tritium and tritiated water as respirable gases.

Natural Tritium	World Inventory - about 70 megacuries
Weapons Tests (90% from fusion explosives)	Inventory - about 3,100 megacuries in 1963. Will decay to natural level by approximately the year 2030.
Nuclear Reactors	Production rate -
Light-Water Type	about 15 to 25 kilocuries per year per 1,000 megawatts electrical energy
Heavy-Water Type	about 600 kilocuries per year per 1,000 megawatts electrical
Liquid Metal Fast Breeder Type (Hypothetical)	about 30 to 60 kilocuries per year per 1,000 megawatts electrical
Production Plants	
Savannah River	about 200 kilocuries per year
Fuel Processing Plants	
Barnwell, South Carolina (Hypothetical)	about 700 kilocuries per year

It is less clear now than it was a few years ago by what number we should multiply the production rates from nuclear reactors. A little over a decade ago, it was projected that nuclear power might account for 430,000 MWe in the United States by 1990 (Unruh 1970b). It is now clear that this is an overestimate.

The figures above reflect actual inventory in only two cases—natural tritium production by nuclear reactions in the stratosphere and weapons tests. The others are only potential in terms of airborne inventory, since the fractions released need to be factored in. The release rates are very idiosyncratic to the installation and activity. In normal operations, except for weapons tests in the atmosphere, only a few percent of the amounts present would be expected to ever reach air, water, or food.

Quite clearly, the contribution of weapons tests has been and is expected to remain for a long time the primary source of tritium in the environment. It is, therefore, instructive to look at the radiation doses to man projected from fallout and nuclear power to the year 2000. (The estimate from nuclear power probably exceeds what will actually occur.) This is shown in figure 10.5.

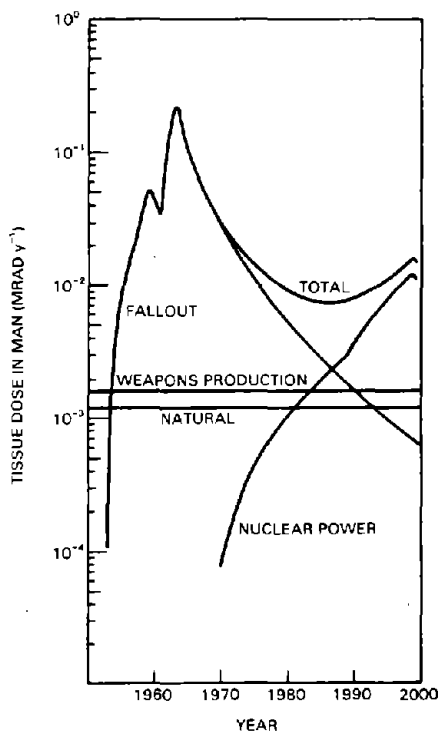


FIGURE 10.5. Projected tissue dose rate from tritium in man. (Redrawn from NCRP 1979. Reprinted with permission of the National Council on Radiation Protection and Measurements, Bethesda, Maryland, copyright 1979.)

As we saw with the noble gases and iodine, the apparently huge inventory results in a yearly (average) dose to man in fractions of a millirad per year. Indeed, the curve seems to be leveling off at around 0.013 mrad per year.

Does this apparently minuscule figure mean we can forget about tritium and consider more important radionuclides? Hardly! These are average doses to the total population based on many assumptions regarding release rates, transfer, metabolism, etc. Individual doses in the vicinity of a facility under accident conditions or even routine exposures close-in can be entirely different.

There are also occupational exposures to tritium. In addition to those possible around the production plants, reprocessing facilities, etc., there is the luminous paint industry. As the saga of the radium dial painters unfolded (chapter 1), the watch and clock makers gradually turned away from radium.^(a) As we saw in chapter 8, they turned briefly to strontium as a substitute radioactive material to activate the phosphors. Later they embraced tritium as a better and safer substitute.

A book prepared by Moghissi and Carter under the aegis of the Bureau of Radiological Health of the U.S. Food and Drug Administration tells the story (Moghissi and Carter 1975). Also a careful field study by Bradley, Blais, and Jones (1971) gives much information resulting from surveys of the watch industry in the New York metropolitan area. It was in the watch industry of Switzerland where two cases of fatal exposure to tritium occurred. A survey of tritium pollution and the amounts of tritium handled in the Swiss industry is given by Krejčí and Zeller (1979).

The result of all of this is that we must know about the biological behavior of tritium. We cannot do a credible hazard evaluation without it. Fortunately (and furthermore), many facets of the biomedical research have great inherent scientific interest with a bearing on all of physiology, biophysics, and toxicology.

C. Biomedical Research with Tritium at the Whole-Animal Level

1. Uptake, Distribution, and Excretion

In chapter 8, we reviewed briefly the early postwar work with animals at Hanford done primarily by Thompson and Ballou. This work concentrated on metabolic turnover of tritium as a tracer in mouse and rat, and comparison to deuterium. It quickly established that absorption was very rapid, distribution to the tissues likewise rapid, and elimination, while grossly rapid, exhibited also some slower phases. These latter were taken to represent elimination from compounds that had bound tritium. In other words, T and HTO resided primarily in body water, but small amounts were bound into organic compounds. Most of this work did not utilize the inhalation route.

As part of the Hanford effort on tritium, Harry Kornberg, manager of the biology department, decided there was no alternative to determining the behavior of tritium in man. This was in the early 1950s. Because of the important role Hanford was playing in the development of the fusion process, security classification, even of biological work, was high. The Hanford and Los Alamos work, which we will review presently, proceeded more or less independently at the time.

(a) The conversion was not complete. Radium is still used some for clock dials, but not for watches.

Anecdotes are best when recalled by the participants. Therefore, I will quote liberally about this effort from a letter from, and interview with, Dr. Kornberg (Kornberg 1982a,b).

Early in the 1950s . . . Hanford manufactured tritium for the yet-to-be-tested fusion bomb. Workers on the production line, isolating and concentrating tritium in hoods and wearing fresh air masks, would suddenly show tritium in their urines after a minor mishap in the process. How were the workers contaminated? I was asked. My first guess was that the fresh air masks were defective and tritium leaked in.

It seemed reasonable that tritiated water should be absorbed readily from the lungs. Dr. Kornberg developed a model that predicted that it should be. However, he wanted direct evidence. Indeed, he did not really believe in the model's prediction that 98% of the HTO would be absorbed. The first experiment went as follows:

With the help of one or two members of the Biology Laboratory, I inhaled a measured amount and concentration of tritium oxide vapor and air from a rubber hot water bag attached to some laboratory tubing. After inhaling the liter of gas in one "normal" breath, I went about my regular duties. As I would do again later, I measured tritium in my urine for about a month. However, to make sure we found how much tritium oxide was absorbed right after I inhaled the vapor, I measured it in my blood first . . . I believed it important to get blood samples very soon after the inhalation—before I exhaled significant tritium and my kidneys transferred it from blood to urine.

The blood analyses showed virtually all of the tritium oxide inhaled absorbed!

Kornberg felt he had proven the point as to how the tritium was contaminating the workers, but the industrial hygienist did not think the mask leaks were sufficient. He postulated skin absorption played a role arguing from the passage of water through the skin. An experiment on anesthetized rat skin indicated possible absorption. Kornberg continues:

I decided we needed to know human skin absorption. So I flowed tritium oxide vapor in air over the skin on my forearm for a measured time, using the same size funnel we used on the rats, and then measured the tritium in my urine with time. This gave me some human skin and additional half-time data. But it was my skin, and it may not have represented normal humans'. I needed more volunteers.

One of them was my good friend, Carl Gammertsfelder, head of the Health Physics Division in the HI Divisions. I placed the funnel on his arm and flowed tritium oxide over it at a concentration and for a time calculated to give him no more than a fraction of the MPL of skin dose or body burden. For a week he turned over to me all his urine, which we analyzed for tritium to calculate skin absorption and body tritium half time. His data were much the same as mine, but something happened.

About a week after the exposure, at a staff meeting in Herb Parker's^(a) office, Carl showed me his forearm. On it was a 3 cm circular area (the size of the funnel) red, inflamed, scabbing, and ugly. I couldn't believe what I saw. I showed Carl my calculations. The exposure was safe! He nodded, smiled, and again showed me his forearm. Herb Parker glared at me.

That night I recalculated again. The dose was safe. What's with the arm?

The next day I saw Carl, and examined his arm. Now I saw. He had used Jean's (his wife) rouge and fingernail polish, he admitted, with glee. Herb was in on it.

(a) Herbert Parker, manager of the Radiological Sciences Department.

The final, and most difficult experiment was one to test skin absorption in a whole man, with no component of inhalation. Kornberg's description follows.

I decided that the only way to get a firm figure on skin absorption would be to expose the entire body of a volunteer, and that I would be the volunteer.

As if made to order, there existed in 100-F area a large box, made of panes of heavy glass. The original use of the big hollow glass cube, measuring about five feet on each edge, remains unknown to me. But it had a crawl-through doorway (which sealed) and some convenient ports. It looked ideal. We had it transported to the laboratory's loading dock, scrubbed it thoroughly, fitted it with appropriate tubes and samplers, and calculated the concentration of tritium oxide needed inside the glass box to give the volunteer who was to sit in the box for one hour a large enough fraction of the permissible body burden to ensure accurate tritium measurements in the body water.

One Saturday morning when the plant was empty of people . . . Chester deLong and I met at the laboratory to set up the experiment. We introduced the tritium oxide and waited until we felt it was well mixed with the box's air by the electric fan we had put in the box. There were two tubes loosely attached to the stool the volunteer was to sit on, ends of which were fitted with one-way valves and protected against contamination. The other ends of both tubes were outside the box. One, the exhaled air tube, simply exhausted into the laboratory air. The other was attached to the laboratory's pressurized air supply through a flask containing cotton to clean the laboratory air to sustain the volunteer.

When all was ready, I removed all my clothes except my shorts, took a deep breath, held it and quickly opened the door and entered the box, closing and latching it behind me. Still holding my breath, I removed the protective covers from the ends of the two tubes, put them in my mouth and tried to inhale. I barely could. Not enough air was coming through! Either I had to get more air through the intake tube or inhale the tritium-oxide-laden air in the box. If I did the latter, I would spoil the experiment for at least a couple of weeks, until most of the inhaled tritium cleared my body water. Frantically I waved one hand up, up repeatedly while the other pointed to the intake tube. Chet deLong, standing just outside the box, understood immediately and ran to the bench in the neighboring laboratory to increase the air. Now so much air came through I momentarily felt like a balloon. Rather than letting the excess air escape and dilute the tritium atmosphere, I breathed rapidly until Chet got back. I motioned for him to turn down the air a bit, which he did, and the valve in the exhaust tube was now able to handle the surplus air.

After an hour the timer rang and I climbed out of the box, took a shower and dressed. For at least the next month I measured the volume of urine excreted and gave samples to Biology's analytical laboratory. The results supported and gave credence to our findings using small areas of skin: The rate of tritium oxide absorption through the skin was the same as tritium oxide absorption via inhalation, at least in my case. Since I then weighed about the same as a "standard man," our data were used for radiation protection procedures among tritium workers at Hanford. (Kornberg 1982a)

The conclusion that skin absorption of HTO is essentially equal to lung absorption has held up to this day.^(a)

At about the same time as the Hanford work with animals described in chapter 8 and the above-described experiments on man, the Los Alamos Scientific Laboratory began biological work with tritium. As a weapons laboratory, Los

(a) The reports of this work were eventually declassified, some of it published in part. But it did not receive the attention it deserved because others had already reported the same thing in open literature publications.

Alamos had ample opportunity to encounter practical problems with tritium exposure. Furthermore, they had in their midst an expert on the physiology of water exchange and water balance, viz., E. A. Pinson, an Air Force Officer assigned to the laboratory. We reviewed the essence of their findings and saw Dr. Pinson's background when we discussed the basic Los Alamos postwar work in chapter 8.^(a) A small segment of the work involved inhalation of T and HTO in the vapor phase.

The now classic review by Pinson and Langham (1957) included the finding, developed earlier at Hanford but not reported immediately, that man absorbs 98% to 99% of the tritium activity when HTO vapor is inhaled. Blood content rose sharply and declined by first-order kinetics with a half-life of about 12 min. Half-time in the body averaged 11.5 days. This work also showed that HTO is absorbed readily through the skin. At equal vapor pressures, HTO passed inward at a rate comparable to that of the insensible perspiration moving out. As Kornberg found, the lung and skin contributed approximately equally to the uptake. Clothing retarded the skin uptake temporarily, but only water-impermeable clothing could prevent the skin absorption.^(b) It was confirmed that any permissible concentrations in air, based on lung uptake, should be halved to account for the skin absorption. (Woodard [1970] raised the question of why the rates should be approximately equal for lung and skin when the alveolar surface area in lung is about fifty times the surface area of the skin. She offers as explanation the fact that the lung surfaces are bathed in fluid and the specific activity of water absorbed is thus less than when HTO enters from the dry skin.)

The work of Pinson and Langham also involved inhalation of T. Very much less is absorbed, on the order of only 0.1%. The inhaled T is gradually converted to HTO, about fifty times more rapidly by the mouse than by man. Absorption and conversion figures were calculated from the amounts in urine.^(c) Figure 10.6 illustrates the contrast in absorption of the two forms of tritium as measured by excretion rates.

Note the large difference in inhaled gas concentration between HT and HTO. The very large difference in absorption of HT versus HTO can be illustrated by noting that equal rates of absorption would occur if HT were inhaled at a specific activity 1,500 times that of HTO. The factor becomes 15,000 for equal rates of appearance of tritium in the body fluids. Thus, most of the tritium of biological significance as a respirable gas is HTO rather than HT.^(d)

Elimination occurred first as tritiated water vapor in the expired air or as T or HT exhaled from the lungs unchanged. This process was very fast and represented essentially the immediate washout. Longer-term excretion after inhalation was slower but still relatively rapid, viz., a quick component with $T_{1/2}$ of about five minutes and a slower component with $T_{1/2}$ about twenty minutes in man (Pinson and Langham, 1957, figure 9). Other half-lives appeared in both

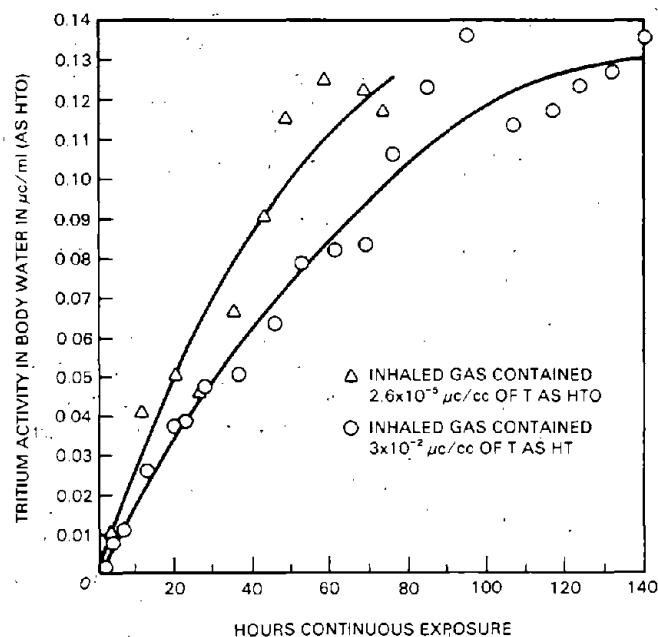
(a) It should be added that Pinson started the ball rolling with a definitive review of deuterium and tritium as tools for water exchange studies (Pinson 1952).

(b) This finding was not a part of the Pinson-Langham work.

(c) It has been demonstrated that the bacteria in the gastrointestinal tract are probably primarily responsible for the oxidation *in vivo* of HT to HTO (see Pinson and Langham).

(d) Since monitoring devices cannot distinguish between HT and HTO, it is customary to assume that any airborne tritium is in the form of HTO. In moist air, T or HT are converted to HTO anyway, but not very rapidly in the absence of catalysts.

FIGURE 10.6. Tritium activity (as HTO) in urine of rats during inhalation of an atmosphere containing HT or HTO. (Redrawn from Pinson and Langham 1957. Reprinted with permission of the American Physiological Society, Bethesda, Maryland, copyright 1957.)



mouse and man, and a fairly considerable variability appears to be common both among individuals and in the same individual at different times. (Remember we saw this phenomenon also with the noble gases. It may reflect the ease with which physiological and environmental conditions can influence these rates.)

Meanwhile, at the Savannah River plant of the AEC and in other studies on man, this same variability was also noted (Butler 1962; Wylie, Bigler, and Grove 1963; Butler and LeRoy 1965; Sanders and Reinig 1968). This was occupational exposure at low levels in general and included over three hundred individuals. Average excretion half-lives varied from twenty-four to eighteen days. Reasons for the variability were easily forthcoming, e.g., forced fluid diuresis, high versus low ambient temperatures, etc.

The excretion data reported from Savannah River showed fairly clearly a three-component exponential relationship to time with half-lives of 6.14, 23.4, and 344 days. The original data and the breakdown according to a three-component model are shown in figure 10.7A and B, taken from Sanders and Reinig (1968).

In a couple of accident cases with higher HTO intake (86 and 46 mCi), the third component was clearly detected in the urinary excretion rates. This had a half-life of several hundred days and may represent the reincorporation of free water tritium released by breakdown of previously incorporated amounts (Woodard 1970).

Toward the end of the Los Alamos work discussed above, the Berkeley group re-entered the picture. Their point of view was primarily the study of exchange phenomena, and they used intravenous or oral administration of HTO. Siri and Evers (1962) worked with rats, pigeons, guinea pigs, and rabbits in which tissue contents were measured directly. This was followed by indirect estimates in man. They concluded that about 0.9 of the exchange occurred with a half-time of one hour while the remaining 0.1 of the exchange had a half-time of ten

FIGURE 10.7A. The observed concentrations of tritium in urine and the least-squares fit of the data. The equation of the line is $U(t) = 742e^{-at} + 2.06e^{-bt} + 0.034e^{-ct}$.

$$a = \frac{0.693}{6.14} \text{ days}^{-1},$$

$$b = \frac{0.693}{23.4} \text{ days}^{-1}, \text{ and}$$

$$c = \frac{0.693}{344} \text{ days}^{-1}.$$

Assuming that all the tritium was initially in the body water, the percent remaining at any time after exposure was obtained by normalizing the above equation to 100 at $t=1$. Thus, $X(t) = 94.72e^{-at} + 0.2776e^{-bt} + 0.004570e^{-ct}$. (Redrawn from Sanders and Reinig 1968.)

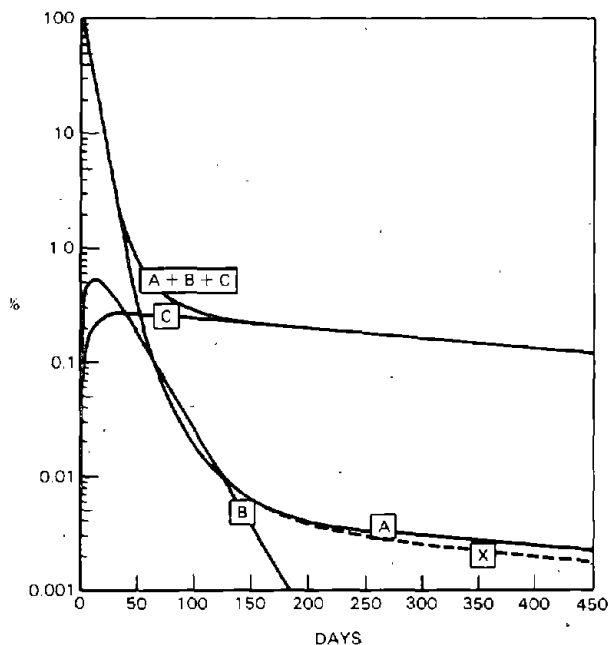
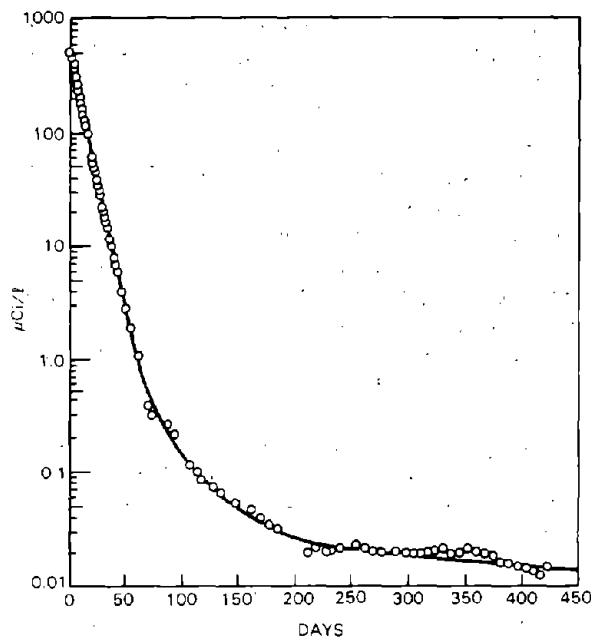


FIGURE 10.7B. The percentage of assimilated tritium in compartments A, B, and C as calculated by an absorbing Markov chain. Curve A represents tritium in body water. Curves B and C represent organic-bound tritium. Curve A + B + C represents total body tritium. Curve X is the percentage of absorbed tritium in body water. (Redrawn from Sanders and Reinig 1968.)

hours. There was a difference between the "tritium space" and total body water determined by desiccation of about 1.5% to 3.5%. In man, the exchange was estimated by concurrent measurements of tritium and antipyrine spaces.^(a) The difference was about 2% and may represent tightly bound tritium.

(a) The drug, antipyrine, is distributed almost entirely in body water.

Results after injection with long periods of observation point to three components in both man and rodents (three, ten, and seventy days in rat and mouse; eight, ten, and four-hundred days in man). The long time components point to some incorporation of T in body tissues.

Snyder et al. (1968) report on excretion rates and calculate doses in the case of an Oak Ridge employee who inhaled HTO.^(a) The excretion could be represented by the same two exponential equations with time terms equivalent to half-lives of nine and about thirty-four days. It is not clear if this case involved enough tritium to detect a third long-term component. On the basis of a two-compartment model developed from these excretion data, Snyder et al. calculate a total dose to the body water. The authors make no comment on the possible reasons they saw two rather than three compartments.

In further experimental work at Los Alamos, Richmond, Langham, and Trujillo (1962) put tritium into their ongoing study of the comparative metabolism of radionuclides by mammals. The intake route was via HTO given intraperitoneally, intravenously, or orally, but it seems likely that the results would apply also to inhalation of HTO, although perhaps not inhalation of HT. Seven species were studied as shown in table 10.5.

TABLE 10.5. Los Alamos Species Correlation Experiment with Tritiated Water

Volume and Turnover of Body Water in Seven Mammalian Species							
Species	Sex	Weight (gm)	Dose (mc)	Route of administration	Exchangeable Body Water (% of body wt.)	Half-time (days)	Water Loss ¹ (ml/day)
Mouse	F	21.4 (24) ³	0.708	I.P.	58.49 ± 3.97 ² (24)	1.13 ± 0.14 (12)	7.22 ± 1.15 (12)
Rat	M	298 (12)	4.329	I.P.	59.61 ± 4.04 (11)	3.53 ± 0.40 (12)	34.54 ± 4.90 (11)
Dipodomys ⁴	F,M	93 (20)	0.850	I.P.	62.20 ± 2.35 (20)	11.82 ± 2.96 (10)	3.75 ± 0.95 (10)
Rabbit	F	3.159 (4)	7.100	I.P.	58.35 ± 5.31 (4)	3.87 ± 0.21 (4)	338 ± 62 (4)
Dog	M	10,582 (5)	1.270	Oral	65.95 ± 1.42 (5)	5.14 ± 0.18 (5)	946 ± 124 (5)
Man	F,M	67,302 (5)	2.000	Oral	55.34 ± 5.31 (5)	9.46 ± 0.88 (5)	2,747 ± 519 (5)
Horse	M	398,533 (3)	142.1	I.V.	65.71 ± 0.72 (3)	8.41 ± 0.53 (3)	21,722 ± 3,247 (3)

¹ From the derivative of $V_t = V_0 e^{-kt}$, when V_0 is the volume of exchangeable body water (ml), t is time O , and k is the rate constant of the exponential function (fractional change per day).

$$^2 \bar{x} \pm \sqrt{\frac{(x - \bar{x})^2}{n - 1}}$$

³ Number in parentheses is the number of animals composing the average.

⁴ Kangaroo rats; maintained in laboratory during experiment on dry pearled barley alone. No other sources of exogenous water were available.

Source: Reset from Richmond, Langham, and Trujillo. 1962. Reprinted with permission of Alan R. Liss, Inc., New York, copyright 1962.

(a) Some of the material may have been ingested. The dose is not known.

The average half-times were within a range from 1.1 days in the mouse to 9.5 days in man, a relatively constant value when the different water loss rates are compared. The kangaroo rat had the longest half-time, about 12 days, which is consistent with its adaptation to desert habitats.

The primary purpose of this study was calculation of daily turnover of exchangeable body water for each species. A correlation between daily water turnover and species weight was established. This has power function characteristics as shown in figure 10.8A. If the correlation is made with body solids rather than body weight, the kangaroo rat comes into line as seen in figure 10.8B.

FIGURE 10.8A. Inter-species correlation between log daily water loss and log body weight. (*Dipodomys* = kangaroo rat.) (Redrawn from Richmond, Langham, and Trujillo 1962. Reprinted with permission of Alan R. Liss, Inc., New York, copyright 1962.)

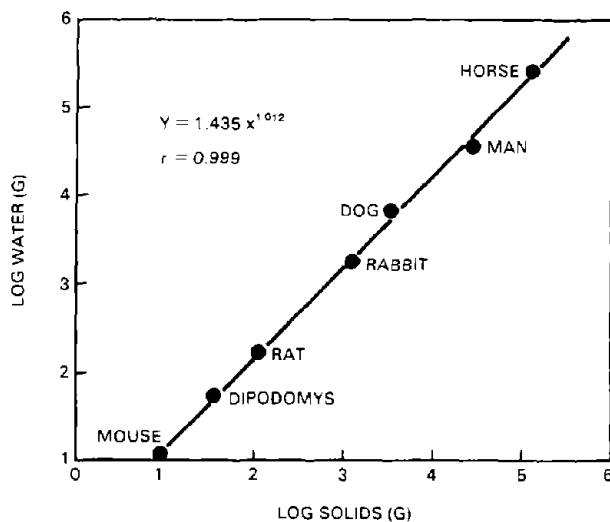
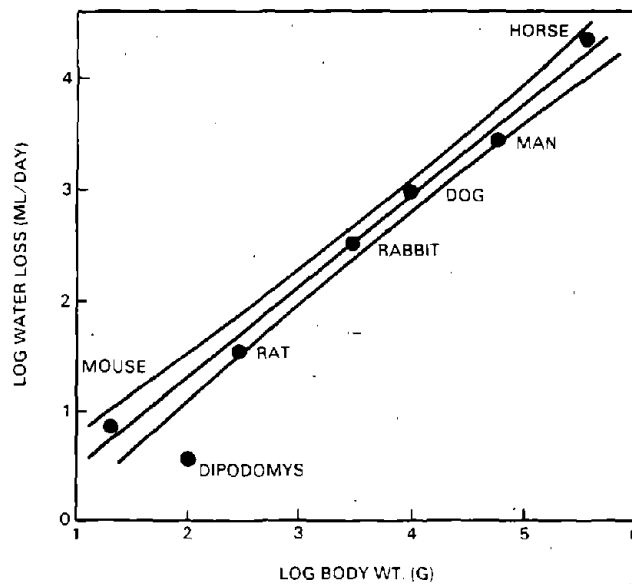


FIGURE 10.8B. Inter-species correlation between log body water content and log body solids content. (Redrawn from Richmond, Langham, and Trujillo 1962. Reprinted with permission of Alan R. Liss, Inc., New York, copyright 1962.)

This information using tritium as a tracer for determining body water has much intrinsic physiological interest. The coefficient of correlation between the two variables in figure 10.8A is 0.985, and the body water turnover is proportional to the 0.80 power of body weight except for the desert rat. From figure 10.8B it can be deduced that the relative partition of water and solids in adult mammals is constant with a value of 1 among the species.

These can be correlated with much earlier work done without radioactive tracers by Adolph (1943). He found a correlation between rate of water intake and body weight of fourteen species ranging from mice to elephants with a power function exponent of 0.88. Urinary output correlated with body weight with a power function exponent of 0.82.

This information has a direct bearing on dose calculations, should such be required for species other than man. Application to maximum permissible concentrations in water is laid out by Richmond, Furchner, and Langham (1960).

The Canadians were especially interested in tritium metabolism because of the large amounts (as much as 300,000 Ci/yr) of tritium produced in their reactors by neutron bombardment of the heavy water (deuterium) moderator. Osborne, at the Chalk River installation, measured absorption of tritiated water vapor in man (Osborne 1979). In work done in the early 1960s, he used volunteers in a chamber so that absorption was through both lungs and skin. The tritium in air concentrations ranged from 0.5 to 50 $\mu\text{Ci}/\ell$, and the exposures lasted from 1.5 to 60 min. The chamber contained HTO introduced by bubbling dried air through a container of tritiated water. In some runs, the subjects wore respiratory protective equipment; in others they did not. Intake rates were around 15 $\mu\text{Ci}/\text{min}$ per $\mu\text{Ci}/\ell$ in the chamber for unprotected subjects and averaged 9.6 for skin. Clothing further reduced the intake rates, but not by very much. Cotton overalls produced a relatively small reduction. It took special protective clothing such as the "PVC" suit to attain real protection as pointed out earlier.

Elimination half-lives in these experiments were 6.4 days for the shorter and 14.4 days for the longer component.

Tritium entering by inhalation or any other route follows body water grossly. Any incorporation into tissue constituents is not uniform. The glycogen and lipid of liver are notably high, and synthesis into reaction components of the glycolytic pathway and the base moieties of DNA has been established by work in a number of laboratories.

Work stimulated directly by nuclear energy problems took place at the Lawrence Livermore Laboratory and was published by Hatch and Mazrimas (1971). This established clearly the incorporation of tritium into many important biomolecules and confirmed the notion first enunciated by Thompson's work at Hanford (see chapter 8) that there is a static component in cells and tissues existing beside the dynamic component so dramatically demonstrated in the earlier years of tracer chemistry.

To accomplish this labeling, parenteral administration is preferred, and many of the experiments have been long-term ones with chronic exposure. The process probably has little significance for inhaled HT or HTO because of the high concentrations that would need to be inhaled over long periods.

As we saw, absorption of tritium through the skin is an integral part of exposure to the gas (T or HT) or tritiated water (HTO). The EPA laboratories at Las Vegas and Montgomery became interested in the skin absorption of various tritiated compounds, especially the many compounds used in luminous paints.

Skin absorption of these was in general lower than HTO (Kaufman et al. 1971; Wawerna 1973). The different compounds behaved differently in terms of skin absorption and probably would also on inhalation.

The work on absorption, distribution, and excretion was the basis for many dosimetric models with varying numbers of compartments. These are well documented in the NCRP report, *Tritium in the Environment* (NCRP 1979), and in the review by Woodard (1970), but can be found also in most of the monographs on tritium. Compartments postulated are body free-water tritium (BFWT), tissue free-water tritium (TFWT), and tissue-combined tritium (TCT). Calculations of integral exposure from TFWT and TCT in microcurie days per kilogram and cumulative radiation dose in rad have been done (e.g., Woodard 1970). A notable feature is the relatively low dose developed from, for example, a single intake of 1 mCi of HTO per kilogram of Standard Man, viz., only 17 rad in two thousand days.

A final rundown (for our purposes) on the kinetics of tritium in man is available in the IAEA 1978 symposium already cited (IAEA 1979):

1. Moghissi, by that time with EPA in Washington, gave biological half-lives of tritium in two former dial painters at surprisingly long times; 340 and 630 days, respectively.
2. Osborne, from Chalk River, Canada, gave new estimated values for skin permeation (not very different from earlier values).
3. Krejčí and Zeller from Radium-Chémie, Ltd., Teufen, Switzerland, told the story of tritium in the Swiss luminous compound industry.
4. Soldat and Baker from Battelle, Pacific Northwest Laboratories calculated worldwide dose from tritium releases from nuclear facilities.
5. The doses to humans were also presented by Eisenbud et al. as a summary of the NCRP report, *Tritium in the Environment* (NCRP 1979). (Authors were Eisenbud, New York University; Bennett, Environmental Measurements Laboratory; Blanco, Compere, and Jacobs, Oak Ridge; Goldberg, Scripps Institution of Oceanography; Koranda, Lawrence Livermore; Moghissi, EPA; Rust, University of Chicago; and Soldat, Battelle, Pacific Northwest Laboratories.)

As part of the rather extensive program on tritium effects mounted at Brookhaven (see next section), Commerford, Carsten, and Cronkite (1977) looked at the distribution of tritium in important biological molecules such as glycogen, hemoglobin, and chromatin. The tritium was given to mice in their drinking water, but, as noted earlier, we would expect similar behavior after inhalation. The exposures started at conception and continued throughout the lives of the animals. The specific activity of hemoglobin was lower than that of the tissue water (more was in heme than in globin) while the activity in chromatin was close to, but always somewhat below, that of tissue water. The specific activity of the carbon-bound hydrogen in glycogen was about half that in tissue water. The authors concluded that, on chronic exposure, the radiation dose to cell nuclei comes more from tritium present in water than from tritium bound to chromatin. Species differences in tritium metabolism led to the conclusion that humans would incorporate less tritium than similarly exposed mice. This has pertinence to inhalation exposure, drinking water exposure, and tritium in nuclear medicine (chapter 20). Estimates of oocyte uptake of deuterium as a surrogate for tritium were also made at Brookhaven (Slatkin et al. 1979).

2. Toxicology of Tritium as a Respirable Gas

a. Acute Toxicity

The generalization that tritium is one of the least toxic of radioisotopes has been confirmed in a general way by the postwar experimental work. Nevertheless, significant radiation hazard problems can exist if tritium is not handled properly. First, there are very large quantities around. Second, it is not easy to separate tritium from water, and large volumes may therefore be possible. Third, the skin absorption route may be forgotten. With these caveats, let us look at some of the aspects of tritium toxicology most pertinent to its intake in gaseous form.

First we should dispel the unfounded statement, which appeared early in the use of tritium, that one breath of tritium gas would be quickly fatal. What was in mind, of course, was a sudden large leak from, for example, a cylinder containing tritium gas. The idea was that the radiation would inflict irreversible damage to the respiratory tract. What was forgotten, of course, was the relatively long physical half-life of tritium and its relatively short biological half-life. Only a small fraction of the inhaled tritium atoms would decay in the lung. A 10-sec exposure to pure tritium gas would result in a dose of only about 6 rem (Evans 1974) and 10 min in a small laboratory room at 10% T in air would yield 40 rem. Furthermore, anyone in a position to receive a lung full of pure or even somewhat diluted tritium gas would be in greater jeopardy from oxygen lack than from the radiation dose. Having disposed of this somewhat hysterical scenario, let us examine the toxicological work.

Anderson and Langham at Los Alamos (1954) made an early estimate of tritium toxicology and concluded, as we might expect from the absorption figures just reviewed, that the hazard from T or HT is about 1/1,000 that from HTO, and the greatest danger from an acute exposure to a mixture of tritium gas in air is ignition of the explosive mixture!

Brues and colleagues at Argonne National Laboratory did one of the earliest experimental determinations of the toxicity of tritium as HTO in a mammalian species (Brues, Stroud, and Reitz 1952). They had been impressed by the many predictions of low toxicity and decided it was time for an experimental test. In addition, they were interested in the possibilities for special effects by selective localization of tritium compounds in cellular structures. They gave HTO intraperitoneally in saline solution to mice. In general, the results upheld the predictions of low toxicity. The thirty-day median lethal dose to the CF1 female mice was about 1 mCi per gram body weight. Calculation of the associated radiation doses indicated no special effectiveness of HTO in comparison to x rays, at least for acute effects.

Furchner (1957), at Los Alamos, whose ingenious approach to dose patterns we saw in chapter 8, did a similar experiment with similar results. Earlier, Anderson et al., also at Los Alamos, determined the LD_{50}^{30} for inhaled HTO to be about 1.5 mCi/ml of body water, which agrees well with the figures obtained with injected HTO.

The pathology in these cases was very unspecific. The effects were similar to acute radiation sickness seen after exposure to x rays or other low-LET external radiation sources.

Meanwhile, the work in man as well as rodents at from 1/100 to 1/1,000 of the LD_{50}^{30} was consistently showing no measurable changes for periods up to as long as two years.

b. Chronic Aspects

Luminizers. The evidence that tritium was not totally innocuous came with jarring impact from the experience with radioluminizers in Switzerland already alluded to (Seelentag 1973). Two fatalities came in workers who had handled from one hundred to several thousand curies of tritium activity over periods from three to six years. They used both the gas and tritiated water. The deaths were due to damage to the hematopoietic system, with symptoms referable to lung damage. For reasons that are not clear, changes in the white cells were much less marked than the decrease in numbers of red cells, as well as hemoglobin, (hyperchromic anemia). The authors classified the disorder as "aplastic panmyelocytopenia."

Monitoring methods for tritium were only under development in the early years of these exposures. Hence, estimation of exposure is difficult. The personnel wore film badges, but readings from these would be essentially worthless. Urine sampling gave the best estimates of dose.^(a) These and some estimates of exposure made before the urinary measurements started gave an overall whole-body dose of about 290 rem. This is for Case 1, an individual who steadfastly refused medical treatment for his developing symptoms. Obviously, the dose to bone marrow must have been much higher. The presence of pulmonary symptoms points also to inhalation as the route of entry for at least some of the tritium. There were two or three other individuals in the same installation who showed symptoms, but they did not progress.

The second fatality occurred in a different installation—one that had used ^{226}Ra and ^{90}Sr before tritium. The fatal case was the person in charge of production for many years. Others were seriously affected in this installation also. The total body dose for this second case was estimated at "less than 1,000 rem within three years."

As part of the elaborate study done by Seelentag, it was estimated that between 10% and 20% of the body tritium was bound in organic molecules, a much higher figure than the 2% or so deduced from acute exposures.

Experimental Work on Chronic Aspects. A substantial amount of experimental work has been done on the long-term effects of tritium exposure, including low levels. Four laboratories may be singled out for their willingness to look into long-term effects of this "innocuous" element: Brookhaven, Lawrence Livermore Laboratory, Los Alamos, and a couplet of Rochester and the EPA Research Center in Research Triangle Park in North Carolina. The Brookhaven work concerns both tritium in nucleic acid precursors (see chapter 20) and tritium entering through drinking water. The Livermore work involves primarily determinations of relative biological effectiveness (RBE) and will be discussed in a separate section of this chapter. The Rochester-EPA work represents essentially a career activity of one man, Daniel F. Cahill, and will be taken up as an entity here followed by the Brookhaven and Los Alamos work.

There is much similarity between the setting and development of Cahill's work with tritium and that of William P. Kirk with krypton, discussed earlier in this chapter. Like Kirk, Cahill was a Public Health Service officer assigned to Rochester for Ph.D. work. He came about five years before Kirk. He, too, chose to work in an area of developing interest to the Public Health Service and of much intrinsic interest.

(a) Excretion of tritium by workers preparing labeled compounds in Czechoslovakia has been reported by Houšková et al. (1973).

After an assignment at the Headquarters of the Bureau of Radiological Health, he went on to the EPA National Environmental Research Center in North Carolina. The work was oriented primarily to problems of population exposures.

The thrust of the work was continuous exposure of rats in utero. Pregnant rats were maintained at constant body activities of HTO by intraperitoneal injection (Cahill and Yuile, 1970, with a preliminary report at the 1969 Hanford biology symposium). There were 101 animals kept at levels from 1 to 100 $\mu\text{Ci}/\text{ml}$ of body water. The calculated associated doses to embryo and fetus were approximately 0.3 to 30.0 rad/day. It was found that T levels in the fetal organs were from 20% to 30% of the average maternal HTO body-water activity.

Progeny were grossly normal. All organs except gonads were normal histologically. However, microencephaly (small head size), sterility, stunting, litter size reduction, and increased resorption were significant findings. These were dose related, but did not occur except at the higher doses. Weight and length of both male and female progeny were statistically reduced at all levels above 20 $\mu\text{Ci}/\text{ml}$. At 1 $\mu\text{Ci}/\text{ml}$, only the length of the progeny was changed (statistically significant at $p < 0.05$ level) and this was an increase.

The authors concluded that a maternal level of 1 $\mu\text{Ci}/\text{ml}$ during pregnancy is consistent with normal progeny except for the possibility of slightly increased length.

Three years later, after Cahill had set up operations at the National Environmental Research Center in North Carolina, the work was extended to the succeeding generation. The levels of HTO were 0.01, 0.1, 1.0, and 10.0 $\mu\text{Ci}/\text{ml}$ of body water (Laskey, Parrish, and Cahill 1973). Administration was via drinking water. Doses were calculated at 0.003 to 3 rad/day. The F_1 litters were delivered naturally, weaned at 21 days, and a dozen males and females continued on the HTO regimen. At 110 days, the females were mated to males from different litters, and exposure continued to delivery of the F_2 generation.

There was a significant reduction (30%) in the weight of the F_1 male testes but no apparent impairment of growth or fertility. In the F_2 neonates, there were reductions in brain weight at the 0.1- and 10- $\mu\text{Ci}/\text{ml}$ level, decreased body weight at 1.0 and 10.0 $\mu\text{Ci}/\text{ml}$, decreased litter size, and increased resorption of embryos at the highest level. Highest levels of HTO content of tissues were reached during the in-utero phases of exposure. Comparison to similar work with x-irradiation indicated comparable but far from identical effects. An important conclusion was that the lifetime exposure regimen produced effects at much lower doses than those required to produce the same effect by in-utero exposure only. There is no way genetic and somatic components could be distinguished.

The minimal level of effectiveness, 0.1 $\mu\text{Ci}/\text{ml}$, corresponds to about 30 mrad/day and the intake to twenty times the maximum permissible concentration in water.

Later work done at North Carolina with collaboration from other laboratories explored the incidence of neoplasms and life-span effects in adults exposed during pregnancy to a greater range of tritium body water contents (1 to 100 $\mu\text{Ci}/\text{ml}$). There was an increased incidence of mammary fibroadenomas at the two highest levels (330 and 660 rad). Also, postexposure life spans were reduced by 14%, 24%, and 22% at 66, 330, and 660 rad, respectively (Cahill et al. 1975a). Rats exposed in utero from conception to birth showed more striking effects. The offspring were sterile after in-utero exposure to 330 and 660 rad (Cahill et al. 1975b). The sterile females had a lower incidence rate of mammary

fibroadenomas than controls, and the life span of both males and females was reduced. The protective effect of sterility did not appear to extend to tumors of the pituitary. Interestingly, the results of this work appear to be in reasonable agreement with effects of x-irradiation of mice at various postconception and postnatal ages. Three hundred rad seemed to be the lowest dose for consistent effects from either tritium or x rays.

In a more biochemical approach, the Research Triangle people, with help from L. N. Parker in the Division of Endocrinology at Harbor General Hospital, Torrance, California, delved into brain neurochemistry following intrauterine exposure to tritium as HTO. The levels and calculated radiation doses were as in the work just quoted. The primary changes were decreases in brain weight and increases in norepinephrine concentrations at doses as low as 66 rad. Exposure in utero to 6.6 rad produced no detectable changes in the biochemical parameters measured (Bursian et al. 1975).

By 1975, Cahill and his coworkers were delving into possible synergistic effects of tritium and a common environmental pollutant, lead. The same technique was used with HTO and/or lead through two generations of rats. The HTO activities were 0, 0.01, 0.10, or 1.0 $\mu\text{Ci}/\text{mL}$, while the lead concentrations were 0, 5, or 50 ppm. Radiation doses from the HTO were calculated to be 3 to 300 mrad/day (0.003 to 0.3 rad/day).

In this work (Cahill et al. 1976), many new parameters were added. Some pups were tested for the development of their startle pattern, the righting reflex, and eye-opening time. Locomotor activity was measured in others using a "residential maze" kept in a sound-proofed room. They also did electroencephalograms and catecholamine assays, in addition to the organ weight observations of earlier work. (This array of observations is refreshing after the single-minded concentration on cancer seen in so much of the work in radioisotope toxicology.)

The results were interesting but not indicative of serious effects. There was a transient body-weight deficit in the F_2 generation of the animals receiving HTO and some elevations of urinary excretion of moieties associated with marginal lead intoxication. Both HTO and lead delayed development of the central nervous system insofar as the administered tests could indicate. When the effects of HTO + Pb are compared to either alone, it appears that the combination was less than additive. Nevertheless, it was concluded that continuous exposures at levels as low as 3 mrad/day from HTO or 5 ppm of lead can yield "biologically important consequences in mammals."

The Brookhaven program was extensive. The four major areas studied are shown in figure 10.9.

Some of the work was very similar to that done by Cahill. An interesting twist was the use of deuterium as a stable isotope tracer for tritium in situations (e.g., primary oocytes) where it would be necessary to maintain the mother on undesirably high levels of tritium in order to get enough incorporation for counting or autoradiography. We will see various facets of the Brookhaven experiments in the balance of this chapter and in chapter 20.

Genetic effects of long-term tritiated water ingestion were studied by Carsten and Commerford (1976) at Brookhaven who looked at dominant lethal mutations in mice. The exposure level was 3 $\mu\text{Ci}/\text{mL}$, and the study was conducted on the second-generation females. There was a significant reduction of viable embryos but no effect on breeding efficiency. Since the system of the experiment was built around the detection of dominant lethal mutations, the authors

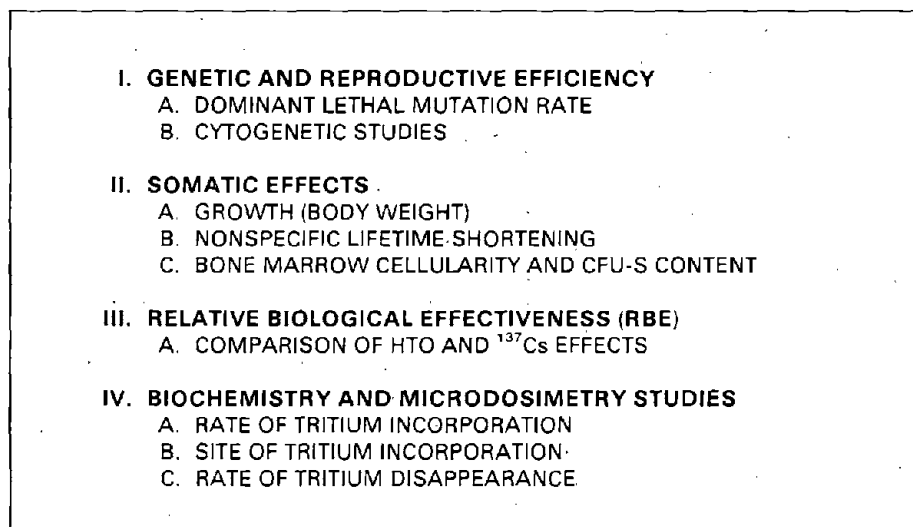


FIGURE 10.9. Brookhaven Tritium Toxicity Program. (Courtesy of Dr. Arland Carsten.)

attribute the changes to genetic rather than somatic processes. Radiation doses, based upon tritium incorporation values, were 0.36 and 0.48 rad/day to ovary and testes, respectively.

Hematological as well as genetic effects were reported by Carsten and Cronkite (1976) at the IAEA symposium on low-level radiation effects. Over 18,000 mouse embryos were examined. The HTO level was, as before, 3 $\mu\text{Ci}/\text{ml}$ placed in the drinking water. Not only was there a significant difference in number of viable embryos but more early deaths in the HTO group. The hematological work concentrated on bone marrow. While there was no change in total cellularity of the bone marrow (leg), the relative number of pluripotent stem cells^(a) was markedly depressed. This began about twelve weeks in the second generation and continued throughout the eighty-week observation period. The radiation doses were about 120 rad to bone marrow for the first twenty-five weeks, but only 31 rad for the second generation ovaries and embryos—and this was an overestimate because of very conservative assumptions.

An experiment on genetic effects of tritium was also conducted at the Biology Division, Oak Ridge National Laboratory. In one of the first experiments using the classic specific-locus mutation technique for an internally deposited radio-nuclide, Russell et al. (1979) gave single^(b) intraperitoneal injections of tritiated water to male mice at 0.75 or 0.5 mCi/g body weight. The estimated radiation dose to the germ cells was 430 and 615 rad to different cell stages of the spermatogonia. The treated mice were then mated to a stock that is homozygous for

(a) Cells with potential for production of many different types of mature cells.

(b) Since only a single injection was given, this experiment does not qualify formally as being in the chronic exposure category. Since the results occur over a generation, we choose to discuss it in connection with the other long-term effects of tritium.

seven recessive marker genes. The induced mutation rate for the offspring of males irradiated in the postspermatogonial stage was 44×10^{-8} per locus per rad, and 15×10^{-8} per locus per rad for irradiated spermatogonial stages. The distribution of mutations induced among the loci by tritium was quite comparable to that seen with x- or gamma-radiation. The mutation rates for the postspermatogonial stages were slightly lower than for external radiation, while those for the spermatogonial stages were higher by a factor of up to two. In view of the problems of the microdosimetry of tritium, the authors caution that the ratio of rates may not be significantly different from 1, but in view of the importance of the spermatogonial stage and of possible dose-rate effects, it might be prudent to adopt a ratio of 2 for radiation protection work (see section on RBE of tritium).

At Los Alamos, Storer et al. (1957) maintained relatively constant levels of tritiated water for five days in mice. The spleen and thymus were found to be atrophied, and the red cells took up less ^{59}Fe than normal cells.

All of this work on chronic exposure to tritium and its effects at the whole-animal level point to effects at fairly low radiation doses.^(a) The Brookhaven people promise work at still lower concentrations of HTO. Extrapolation to humans is difficult because of the differences in water turnover rate, but the information should be fed into any analysis of the environmental consequences of tritium releases.

It should be emphasized again that the route of administration for much of this work was not inhalation. However, as stated earlier, we have assumed that the great mobility of T in the forms we have been discussing makes the route of administration of little consequence. This obviously may not apply to every detail, and it certainly does not apply to luminous paint compounds containing tritium.

D. Toxicology of Tritium at the Cellular Level

The extremely low energy of the beta emission of tritium poses some special problems concerning effects at the cellular level. Since the mean range of tritium beta particles in water is only $0.69 \mu\text{m}$, and the maximum range is $6 \mu\text{m}$, a significant fraction of the deposited energy can be absorbed in single cells, even single cell nuclei. A reference cell nucleus is frequently taken as about $8 \mu\text{m}$ in diameter. The only other common isotope with so much energy deposition in a small volume is ^{125}I , which is special because of the involvement of Auger electrons.

To a degree, the concerns here are grossly comparable to those we saw in chapter 9 as the "hot particle problem." However, here we are at a more micro level. Concern was exacerbated by the growth of uses of tritium (and iodine) for labeling cell macromolecules, including the precursors of DNA. It became clear rather early that tritium-labeled thymidine inhibits the growth and survival of cells in tissue culture, and of ascites tumor cells; causes changes in cell ploidy; causes chromosome aberrations in plants, leukocytes, and regenerating rat liver cells; produces mutations in the germ cells of mice and in bacteria; and can

(a) Remember the doses given are cumulative doses occurring over a significant period.

induce cancer (Dewey, Humphrey, and Jones 1965). The work was done largely at the centers for tissue culture and cellular radiobiology, e.g., M.D. Anderson Hospital in Houston, Brookhaven National Laboratory, Lawrence Livermore Laboratory, Oak Ridge National Laboratory, University of Rochester, and Ohio State University. Gradually, nearly every radiobiology and nuclear medicine laboratory was either concerned with the problem or actively experimenting on some aspect of it because of the ubiquitous use of labeled nucleic acid precursors.^(a)

An additional concern was the possibility of a transmutation effect, i.e., a distortion of the chemical bonding, and thus molecular configuration, of biologically important molecules by the transmutation of hydrogen—a very reactive element—to helium—a very unreactive element. It took very careful study in many laboratories, especially Brookhaven and some laboratories abroad, to put this concern to rest. Since the problems and experimental investigations are much more pertinent to the uses of tritium in nuclear medicine than to inhalation problems, we will reserve the full story for chapter 20.

Suffice it to say here that the preponderance of evidence is that all effects can be accounted for by the radiation dose. Transmutation effects are negligible, except in the possible case of one particular labeled nucleic acid precursor.

E. The Relative Biological Effectiveness of HT and HTO

We enter here an area that has commanded large investments of time and energy in radiobiology. We have had little to do with it so far in this book, and, therefore, a short background statement is in order. The RBE problem concerns the fact that the same absorbed dose of ionizing radiation has different degrees of effectiveness, depending upon the "quality" of the radiation. The most common differences in "quality" are between photon radiation, such as x or gamma rays and beta particles on the one hand and neutrons, alpha particles, fission fragments, and the like on the other. A ratio called the relative biological effectiveness can theoretically be derived for any comparison of effectiveness of different radiations. The RBE is defined as:

$$\text{RBE} = \frac{\text{Dose of reference radiation}}{\text{Dose of experimental radiation}}$$

where the doses measured are those required to produce *the same degree of the same biological effect in a given organism*.

Thousands of determinations of this ratio have been made for organisms ranging from bacteria and viruses to the primates using a large number of biological endpoints. A tradition has grown to use low linear-energy-transfer (LET) radiation, such as radium gammas or 250-kv x rays, as the reference radiation. The fact that internally deposited radioisotopes differ from each other in ways other than radiation quality, e.g., site of deposition, half-life, movement within the body, etc., means that determination of a "pure" RBE as defined above is usually not possible. The toxicity ratios we discussed in chapters 7 and 8 have sometimes been termed relative biological effectiveness factors, and there is no

(a) We have arbitrarily considered genetic changes caused by HTO in the section on whole organism studies because it is in the whole organism that we see the results of the mutations. Obviously, the process itself is a cellular-level phenomenon.

reason the term cannot be applied except for the tradition that has grown up around the definition as given. Because of the possibility of determining relative effectiveness of two types of radiation uncomplicated by half-lives, distribution of isotope, etc., the bulk of the experimentation with RBE has been done using external radiation sources rather than internal emitters.

The now classic report of R. E. Zirkle at Chicago, published in the Met Lab report series (Zirkle 1943), established that the differences in effectiveness of the same dose to different radiations could be correlated with their ion density or "specific ionization." Subsequently the term "specific ionization" was replaced by the term "linear energy transfer" and the relative effectiveness predicted from the LET. Further discussion would carry us too far into basic radiobiology for the purposes of this book. The interested reader can find ample discussions of the subject in any of the numerous texts or monographs in radiation biology.

As we will see in chapter 16, account is taken of the differences between radiation qualities in calculating effective doses by introduction of a factor called the quality factor or "Q."^(a) Its value was derived largely from work with external sources, including another classic piece of work by Zirkle using the alpha particles from ^{210}Po .

Much interest in the possible RBE and derivable Q factor for tritium beta radiation arose because its very-low-energy beta particle had relatively high values of LET compared to most beta emitters. These might conceivably produce greater effects per unit of absorbed dose than the higher-energy beta emitters, as we hinted at earlier.

A first indication of results came from Argonne National Laboratory, where Brues and his colleagues followed up on the acute toxicity work already reviewed. Jennings and Brues (1951) compared toxicity of HTO in rats to known values for x-irradiation and found an RBE close to 1.

A second indication came from Hanford, where Getzendaner, Fujihara, and Kornberg (1953) reported an RBE of 2 for inhibition of growth of the bacterium *Lactobacillus casei*.

However, it was at Los Alamos that the first concentrated work was done. The laboratory already had a broad program on RBE, and there was also considerable interest in tritium for the reasons we saw earlier.

The early work done by Furchner and Storer in 1953 and cited by Storer et al. (1957) indicated an RBE of 1.4 to 1.6 for depression of the uptake of ^{59}Fe by rat red blood cells. The comparison was between tritium and gamma rays from radium or ^{60}Co .

Spalding, Langham, and Anderson (1956) determined the RBE of tritium in affecting growth of the root of the broad bean (*Vicia faba*). (This was the system used with great effectiveness over almost two decades by L. H. Gray in England.) They grew the bean roots in culture cells that allowed immersion of the root system in HTO or exposure to x-irradiation from a 250-kvp Maxitron machine. The actual energy to the bean roots was about 175 kvp.^(b) A graph of the response as a function of dose showed the points for tritium irradiation and x-radiation essentially superimposable. In other words, the derived RBE was 1 (given as 1.0 ± 0.06).

(a) This is derived from the RBE by a judgmental process and is strictly for use in radiation protection. Conversely, the term RBE is now strictly for use in radiobiology.

(b) Several exposure arrangements were tried, but the results were not materially affected.

Worman, Turney, and Lotz (1954), also at Los Alamos, used thymic atrophy in the mouse and compared HTO to ^{226}Ra gamma-rays delivered at a constant rate for five days. The RBE value was about 1.5.

The ingenious experiment by Furchner (1957) at Los Alamos already described and referenced in chapter 8 compared tritium to ^{60}Co gamma rays, which were given with an exponentially declining dose rate to imitate the decay and excretion kinetics of HTO. The criterion was lethality using CF1 mice. In this system, the RBE appeared to be about 1.7.

The provisions for an external dose rate that imitated kinetically the exponential decrease of the radioisotope lent special credence to the RBE value for this experiment.^(a)

In their monumental analysis of RBE studies in mammalian systems, Storer et al. (1957) at Los Alamos quote work involving splenic atrophy, thymic atrophy, and depression of ^{59}Fe uptake. The RBE values were 1.3, 1.5, and 1.6, respectively. Graphs showing the relationships of splenic weight loss, thymic weight loss, and uptake of ^{59}Fe to radiation dose are shown in figure 10.10A, B, and C, taken from the Los Alamos work.

Note the almost identical slopes of the trend lines over a considerable range of dose, and thus constancy of the ratio, i.e., RBE, with dose. This is far from universally true. It is more likely with radiations of low and roughly comparable LET, but, as we shall see, such constancy does not apply to even all of the tritium work. The Los Alamos workers were very skilled, but we have to admit to there being a certain element of luck in the beauty of these first experimental results.

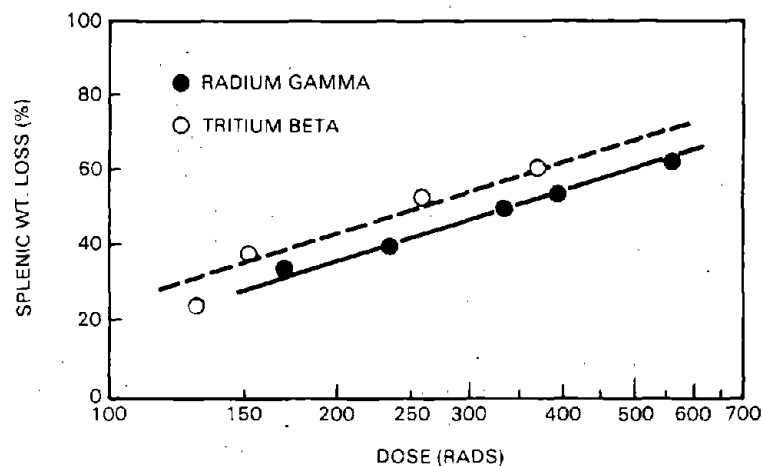


FIGURE 10.10A. Splenic weight loss in mice at 5 days as a function of dose of tritium beta-particles and radium gamma-rays. (Redrawn from Storer et al. 1957. Reprinted with permission of Academic Press, Inc., Orlando, Florida, copyright 1957.)

(a) The only other experiment extant with a similar exponential decrease of external radiation dose for the reference radiation is one by Lambert in the United Kingdom (1969). He used the ability of intermediate spermatogonia to divide twice as the criterion of effect. The RBE against HTO was from 2.0 to 2.4.

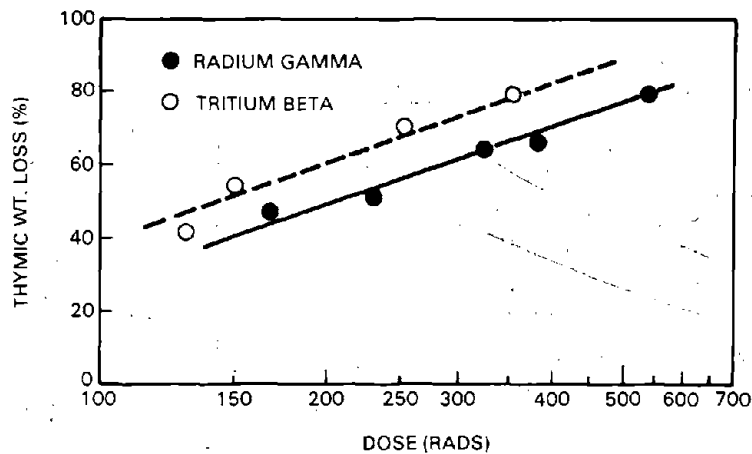
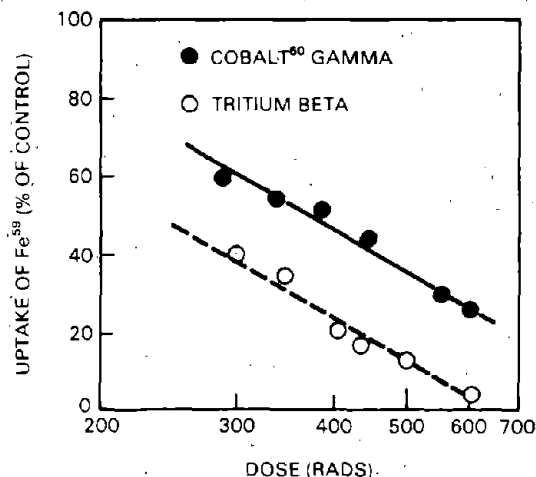


FIGURE 10.10B. Thymic weight loss in mice at 5 days as a function of dose of tritium beta-particles and radium gamma-rays. (Redrawn from Storer et al. 1957. Reprinted with permission of Academic Press, Inc., Orlando, Florida, copyright 1957.)

FIGURE 10.10C. Uptake of Fe^{59} by rat red blood cells as a function of dose of tritium beta-particles and radium gamma-rays. (Redrawn from Storer et al. 1957. Reprinted with permission of Academic Press, Orlando, Florida, copyright 1957.)

Thus, the early work suggested that tritium beta particles may be slightly more effective than classic low-LET radiations. For radiation protection purposes, a quality factor (chapter 16).



The idea that the value for the RBE for tritium is greater than 1 was strengthened by the results of Lambert, for example, who indicated that the nucleic acid precursor, tritiated thymidine, might be more effective than HT or HTO.

A summary of the RBE data including their ranges of uncertainty is shown as figure 10.11.

Much more work was done, subsequently at the cellular level at a variety of institutions. These showed a greater range of values than the work quoted, including many that approached 1. Examples of the latter are the production of chromosomal aberrations in Chinese hamster cells exposed in vitro to HTO and ^{60}Co gamma rays by Dewey, Humphrey, and Jones (1965) working at Houston (RBE values 1.2 or 1.06), and clonal growth of HeLa cells at a dose rate of 32 rad per hour by Hall, Oliver, and Bedford (1967).

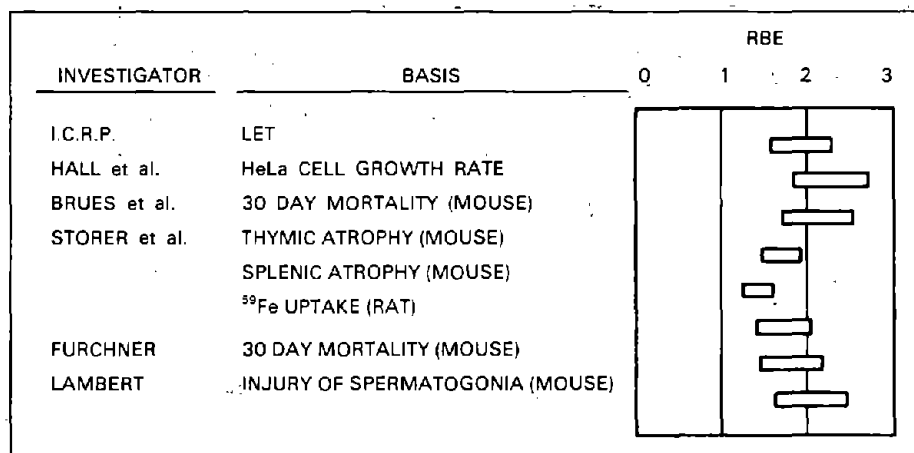
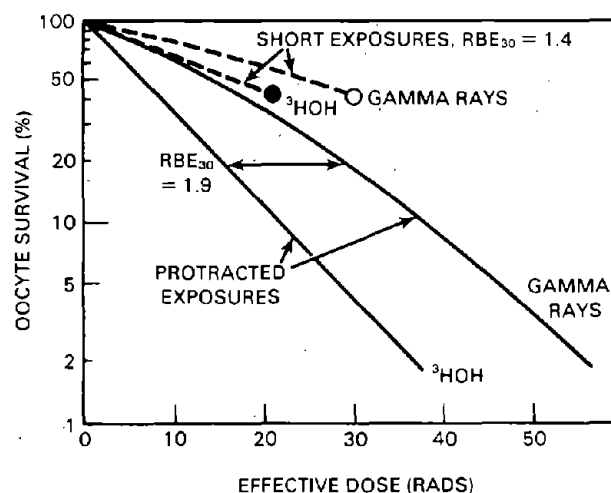


FIGURE 10.11. The ranges of uncertainty in RBE for tritium; data of various investigators. (Redrawn from Johnson 1973. Reprinted with permission of Messenger Graphics, Las Vegas, Nevada, copyright 1973.)

Indications that the RBE was subject to variation depending on conditions appeared in both the work with HeLa cells and the work with bean roots done by Hall and colleagues. Changes in dose rate of the reference radiation could produce variations by a factor of two. Further indication of variability under different conditions was seen in work at Berkeley by Dobson (1976), who studied the survival of oocytes from mice that had been treated for shorter (e.g., five days) or longer (e.g., thirty-three days) periods with HTO or ^{60}Co gamma rays. An example of the results taken from Dobson and Kwan's 1976 work is shown as figure 10.12.(a)

FIGURE 10.12. Oocyte responses to ^3HOH and ^{60}Co gamma-rays given in short (5-day) and protracted (33-day) exposures compared. (Redrawn from Dobson and Kwan 1976. Reprinted with permission of Academic Press, Inc., Orlando, Florida, copyright 1976.)



(a) The marked variability of RBE values with choice of biological endpoint is not by any means limited to tritium. Both it and effects of dose rate and of total dose are ubiquitous. Indeed, they have to be when the underlying radiobiology is appreciated.

Even before the work of the 1970s, those responsible for recommendations in radiation protection had begun to have second thoughts about the use of a quality factor of 1.7 for low-energy beta particles. Two definitive reviews and critiques appeared in the late 1960s and early 1970s; one by Vennart (1968) at the Radiological Protection Service in the United Kingdom, the other by Johnson (1973) domiciled at the State University of New York at Stony Brook, but obviously in close touch with the Brookhaven group. Both conclude that the RBE values have so much range and include so many uncertainties that no value except 1 can be supported for radiation protection work. This applies even to the nucleic acid precursors and includes transmutation effects (Feinendegen and Bond 1973).

Thus, in a sense, the field reversed itself in its interpretation of the findings.^(a) By the time of the NCRP report on basic radiation protection criteria (NCRP 1971) we find the following footnote to the table giving practical quality factors:

In 1966 the ICRP^(b) recommended a value of 1.7 for the QF of low energy electrons or protons. We believe that a rounded value of 1 is more commensurate with the accuracy of our knowledge and the requirements of radiation protection. (In 1969 the ICRP amended its 1966 recommendations, specifying that the QF should be taken as 1 for all β^- , β^+ , e^- , γ and x radiations, and for conversion electrons). (NCRP 1971, table 5)

Work from Oak Ridge published in 1976 compared tritium and plutonium in producing chromosome aberrations in *Chironomus riparius* (Blaylock and Trabalka 1976) with the surprising finding of a relatively lower effectiveness of plutonium in this system than is usually expected from its RBE of 10 to 20 or more. However, in general, the work with tritium in no way puts it in the class with plutonium as a toxic agent.

Carsten and Cronkite, at Brookhaven, compared late effects of single x-ray exposure, chronic ^{137}Cs gamma exposure, and chronic tritiated water ingestion in mice. The work is fairly recent, reported at the 1979 IAEA Symposium on *Biological Implications of Radionuclides Released from Nuclear Industries* (Carsten and Cronkite 1979). The criteria were primarily hematological. It was not possible to determine whether there is a significant difference in effectiveness of the two chronic modalities. The authors conclude "indications are that they are similar."

Some work has continued on the RBE for tritium beta particles. There are grumblings from the "pure" scientists that the preponderance of evidence indicates that tritium beta particles are more effective than very low-LET radiations, just as there is growing evidence that 250-keV x rays, with a higher LET than radium gammas, are slightly more effective (by perhaps a factor of 1.3). There are indeed ample theoretical reasons that particles in the LET range of the beta particles of tritium, especially if the tracks happen to bend back upon themselves, should deliver a higher local dose than radiations with minimal LET. However, those making recommendations for radiation protection are equally disposed to grumble about the validity of the RBE data and to doubt that there is evidence enough to support any Q value but 1.

(a) Note that this applies only to the practical use made of the RBE values and in no way reflects on the interest in and importance of the findings toward understanding radiobiological mechanisms.

(b) ICRP 1966.

Despite these differences, which are more in point of view than anything else, the work on the RBE for tritium can be viewed as of real interest and significance. It brought many of the radiobiologists who had never worked much with radioactive isotopes—at least vis-à-vis internal emitter toxicology—into the field. It brought to light some quite basic and important scientific questions, only some of which centered around HT and HTO.

F. Work with Tritium Abroad

Throughout this book, the need to concentrate on U.S. work has frequently caused us to give short shrift to meritorious work in other countries. Since the bulk of the work with tritium was done in the postwar years, and it has attained great popularity in tracer chemistry, a large effort was expended everywhere on questions of its toxicity. Thus, we are having to by-pass an especially large amount of good work abroad on this subject.

We did glimpse briefly the work with the Swiss luminizers and some of the U.K. work that tied most closely to subjects we were discussing. A review of the several symposia and monographs cited in section IV A will give a reasonable picture of what went on in other countries. In addition, special mention should be made of work that the Commission of the European Communities sponsored, viz., a full review of tritium much like the one prepared for the AEC by Jacobs (1968) but more biomedical in emphasis. This was prepared for the Comitato Nazionale per l'Energia Nucleare (CNEN) by Silini, Metalli, and Vulpis (1973). Also, special mention should be made of the enormous effort in the Soviet Union, represented by a book edited by Moskalev (1968) and several papers on tritium in the 1966 compendium also edited by Moskalev (1966, section III).

The CNEN document addresses both metabolism and toxicity of tritium in mammals and applies the information to dosimetry. They make even more of the "special problems" associated with tritium dosimetry than we have. They take up the physical problems of the short track length and "microscopic physical heterogeneity" along the lines we have already discussed. In addition, they introduce the concept of "microscopic biological heterogeneity." This is based on possible differences in tritium concentrations in particular cellular or subcellular components and the consequent variations in the structure irradiated. They emphasize evidence from microautoradiography (which we have had to treat very lightly) that shows possible inhomogeneous disposition of tritium within nuclei and chromosomes at the metaphase stage of cell division and muse on the fact that such differences do not seem to account for the differences in dose estimates. The majority of experimental work quoted in this document is U.S. work. It appears that the CNEN laboratories did not themselves engage deeply in biological research with tritium.

The work from the Soviet Union, on the other hand, covers the entire field with detailed experimental studies. The research that deals with the same problems as we have described for the U.S. work comes to approximately the same conclusions. Their RBE experiments tend toward ratios between 2 or 3 rather than between 1 and 2. They show no disposition to use a lower figure for radiation protection. In the chapter on maximum permissible concentration of tritium, they use an "RBE coefficient" of 3 (Moskalev 1968, p. 353).

The USSR work goes into much more detail on histopathology, even though the picture closely resembles the radiation syndrome from external sources.

Also, they add effects on immunological reactivity, effects on enzymes, and studies on embryos, fetuses, and newborn, with results fairly similar to the U.S. work.

The work abroad and that in the United States agree in general, but some interpretations differ.

V. Radioactive Carbon Dioxide

A. Overview

"Atmospheric carbon dioxide is the major source of the carbon in all living organisms" (NCRP 1985). Despite this truism, atmospheric radioactive carbon dioxide (with ^{14}C) is of almost no practical importance in pulmonary radiotoxicology. The reasons for this apparent contradiction are manifold. Some of them are:

1. A large portion of the carbon in the atmosphere gets incorporated into plants by photosynthesis. The radiocarbon is distributed among the many products of photosynthesis.
2. The major intake of radiocarbon by man is by ingestion, either of plant material or of animal products that have incorporated the carbon from ingestion of plant materials.
3. By far the largest reservoir of carbon is the oceans. Transfer to man involves many steps, of which inhalation is quantitatively a very minor one.
4. Inhaled radioactive carbon dioxide is diluted in the lungs by the carbon dioxide always present in the lungs. Its specific activity is materially reduced thereby.
5. The long half-life (5,730 yr) and low energy (0.156-MeV maximum beta energy) of ^{14}C mean that few of the inhaled radioactive atoms decay in the lung or even in the body if absorbed, and those that do decay contribute only small radiation doses.

Despite knowledge that radiocarbon was produced by neutron activation processes in fission reactors and fission weapons, the facts enumerated above must have convinced the biomedical teams of the Manhattan Project that they had more urgent problems to consider than the possible inhalation of radioactive carbon dioxide. Thus, although the tracer uses of ^{14}C continued and grew during the war, there was very little toxicology done. Even in the post-World-War-II years, when it was evident that much more radiocarbon could be produced in the fusion process, biomedical work remained sparse insofar as radiotoxicology was concerned.

There are a few calculations and one or two experiments that should be described because of their direct bearing on potential inhalation problems. We will examine these here with the understanding that the enormous efforts that went into environmental aspects of the ^{14}C problem belong in later chapters.

B. Sources of Radioactive Carbon Dioxide

As we saw in chapter 5, long-lived radiocarbon (i.e., ^{14}C) was prepared by Kamen and Ruben in 1940 by bombarding graphite enriched with ^{13}C with low-energy deuterons. Because of the key role of carbon in biochemistry, the new radioisotope became instantly popular for applications in tracer chemistry.

(chapter 5). Libby (1955) first identified the presence of ^{14}C in nature. It is now well known that it is produced at a roughly constant rate, except for changes in ambient flux, by reactions of cosmic ray neutrons with a number of elements, the most important being nitrogen, oxygen, and carbon, in that order. As the atomic energy project developed, it was obvious that ^{14}C was produced at many points in fission reactors and in both fission and fusion weapons. The world inventory of radiocarbon was increased considerably by the atmospheric testing. Whereas the average production of ^{14}C by interaction of cosmic rays with elements in the upper atmosphere is about 0.038 MCi/yr, and the global inventory is about 3.8 MCi in the atmosphere,^(a) about 9.6 MCi of ^{14}C have been introduced into the atmosphere by thermonuclear explosions alone.^(b) The maximum level, at about 1963, was 350×10^4 Ci in the stratosphere and about 275×10^4 Ci in the troposphere.

All nuclear reactors produce ^{14}C . Like our estimates for tritium, the projected amounts are subject to considerable uncertainty because of imponderables regarding the future development of nuclear energy. The NCRP report (1985) declares that the bulk of the releases from reactors are to the atmosphere rather than to liquid effluents. The same is true of fuel processing. The amount expected to be released through 1990 is 235 kCi with 12.1 kCi released by the nuclear industry through 1970. The graphite-moderated and heavy water reactors account for more than the light water cooled reactor or the fast reactor. It can be seen that this amount is much smaller than that released by atmospheric testing of weapons.

A final source of radiocarbon is in the labeled compounds used in medical and biological research. The U.S. Department of Energy estimates the amount as between 100 and 500 Ci annually.^(c) This carbon is unlikely to be available for inhalation unless incinerated. However, we must remember that the metabolism of carbon compounds by most organisms of interest to us results largely in carbon dioxide and urea, which are returned to the environment and reenter the cycle.

Obviously, in many respects the source-term aspects of radiocarbon resemble those we reviewed for tritium. However, it is even more an environmental distribution problem and even less a direct inhalation problem than is tritium.^(d)

C. Uptake and Retention

In essence, the behavior of ^{14}C follows stable carbon, although there is a small isotope effect in the synthesis of some compounds. The processes of uptake and retention of ^{14}C are, of course, regular grist for the mill of biochemistry. But the source is characteristically food or parenteral administration. Thousands of experiments bear on this aspect. By contrast, very few experiments have been aimed at uptake and retention of inhaled radiocarbon. Principal among these is work from Argonne National Laboratory.

(a) Do not forget the ultimate sinks are the oceans and rocks.

(b) The yield is primarily from fusion weapons.

(c) Actual amounts are proprietary information of the pharmaceutical industry.

(d) If this is the case, why have we bothered to review the subject? The primary reason is that we need to know why inhalation is considered unimportant, and the story provides important background for our environmental discussions to come.

The work was initially aimed at hazard evaluation, but this aspect gradually became secondary to the development of knowledge of the metabolism of inhaled carbon. Brues and Buchanan (1948) developed a "flushed chamber" apparatus, which exposed mice to atmospheres of $^{14}\text{CO}_2$ in nitrogen/oxygen introduced from cylinders. This was a static atmosphere, which was renewed by periodic flushing.

It was soon apparent that absorption of $^{14}\text{CO}_2$ from the lung was very efficient in spite of the mass movement of metabolically produced CO_2 in the other direction. Equilibrium values in the blood bicarbonate reflected faithfully the specific activity of the alveolar CO_2 . Since alveolar pCO_2 is not changed much by reasonable changes in inhaled CO_2 concentration, this meant reasonably constant blood ^{14}C bicarbonate. Only if the inhaled pCO_2 was high enough to cause hyperventilation was the rate of absorption accelerated.

Removal rates on cessation of exposure were essentially a mirror image of the uptake, except for a small fraction with a longer retention time.

Autoradiographic work with chick embryos showed rather long retention of the incorporated ^{14}C , since it had been built into growing tissues including bone.

This immediate postwar work was expanded on by Buchanan (1951). He used a more complex exposure system, which held the pCO_2 and the specific activity constant. Again, the original purpose was radiotoxicity. Finding none, they used the system as an excellent way to introduce labeled carbon in a steady state situation. The exposure levels ranged from 0.03% to 5% CO_2 in air. Exposure lasted as long as forty days, and retention was measured out to fifty days after termination of exposure. He determined the specific activities of many tissues and compared them to the specific activity of the inhaled air. The value of this ratio ranged from zero at the outset to about 10^{-4} after forty days. The equilibrium level of specific activity never exceeded 10^{-4} , or about 0.01% of the specific activity of the air breathed by the mice, an unexpected result. There were significant differences among the tissues.

These results led S. R. Bernard (1973) at Oak Ridge^(a) to a careful analysis and development of new metabolic models for ^{14}C . He showed that the average mouse inhales only 0.005 g of carbon per day, whereas it eats 4 g of food a day, one-fifth of which is carbon. This yields 0.8 g of carbon per day from food or a factor of $0.005 \text{ g}/0.8 \text{ g}$ or roughly 10^{-2} . This accounts for one-half of the 10^{-4} factor found by Buchanan. A second factor of 100 is deduced by considering that alveolar air normally contains 3% to 5% CO_2 or about one hundred times the concentration inhaled (0.03%). These two together round out the factor of 10^{-4} found by Buchanan. (Bernard goes on to apply the model to calculations of maximum permissible concentrations [now "derived air concentrations"] and suggests that figures derived from the old models may be substantially in error.)

Buchanan and Nakao (1952) made sure that equilibrium conditions prevailed by having rats and mice continuously inhale labeled CO_2 . Relative specific activities of soft tissue and bone reached about 70% of the specific activity of alveolar CO_2 , while arterial blood reached full equilibrium. The specific activity

(a) Of the major U.S. laboratories, Oak Ridge and Argonne have shown more activity in this particular aspect of radiocarbon behavior than any other. Those concerned at Oak Ridge were either interested in dose estimation and standard setting (e.g., Bernard, Snyder) or in environmental aspects (e.g., Rohwer, Killough).

of alveolar CO_2 was always much lower than ambient, in agreement with Buchanan (1951). Soft tissue labels were lost quickly, but some fractions of the bone carbonate retained the label for significant periods. This was a function of age and duration of exposure. Approximately 30% of the bone bicarbonate was replaced in twelve days, but only 45% was replaced in three months. These longer retention times of significant fractions raised some questions about the innocuousness of ^{14}C . However, the then-extant maximum permissible concentration of $^{14}\text{CO}_2$ for continuous exposure (about $10^{-6} \mu\text{Ci}/\text{m}^3$ of air) probably was sufficiently conservative to allow for this. Buchanan and Nakao calculated a much higher allowable concentration.

The fraction of radiocarbon retained after injection of $\text{NaH } ^{14}\text{CO}_3$ into mice was well described by a power function of time (Skipper as quoted by Bernard 1973). The function was $1.4t^{-1/2}$, a relatively slow loss rate compared to the noble gases and the bulk of inhaled tritium. However, it appears that only 1% of inhaled ^{14}C is taken into the blood (i.e., remains there for any significant period) in the mouse. If this holds for larger animals and man, it would require very large exposures to reach significant doses. There are apparently no experiments, except tracer experiments for other purposes, in larger animals or man to check out these low incorporation figures. If they were to be considerably higher in other species, the fairly long retention time (for a "gas") could lead to some more consequential doses. It is surprising that more work has not been done in this area.

It is clear from a large amount of biochemical and tracer work that respiratory CO_2 can enter into all organic components of the body and tissues except for a few substances that are not synthesized by the body. However, the compartments in which the compounds are produced are, except for some parts of bone, subject to rapid turnover. Thus, the labeled carbon is readily lost to either expired air or excretion as urea. One or two days suffice to wash out almost all of the radiocarbon taken in (Hellman et al. 1953, Baker et al. 1954 as quoted by NCRP 1985). The exception is mineral bone, which may have specific activities after inhalation of radioactive carbon dioxide twenty-six-fold higher than the organic carbon (NCRP 1985).^(a)

D. Effects

Essentially no direct experimental work has been done with inhaled radioactive carbon dioxide at levels that would produce radiation effects. Such would be impossible because of the marked effects of CO_2 on respiration. We are again relegated to the computational approach. Calculation of doses based on equilibrium with present global environmental levels of ^{14}C predict doses of about 1.5 mrem per year to the individual member of the population. Only a small fraction of this would be from inhalation. Even with very significant localized events, very large factors and very special conditions would have to enter to make the inhalation dose take precedence over others.

Additionally, there is little likelihood that the mean dose will increase with time unless very large additions to global radioactivity occur. This is because of the constant addition of stable carbon (^{12}C) from the burning of fossil fuels in one or another form. This keeps the specific activity down and essentially unchanged.

(a) But there is more organic carbon than inorganic carbon, even in bone.

The calculated maximum permissible air concentration for ^{14}C as $^{14}\text{CO}_2$ is $4 \times 10^{-6} \mu\text{Ci}/\text{cm}^3$ (with fat as critical organ), while that for tritium is $5 \times 10^{-6} \mu\text{Ci}/\text{cm}^3$ with body tissue as critical organ (ICRP 1959)—very similar.

The same concerns occur regarding genetic change with ^{14}C in an incorporated radionuclide as we saw with tritium. Much less has been done than with tritium. Hence, we will have to content ourselves with the almost certain knowledge that inhalation would contribute little in any event. If our mutual patience holds, we will look briefly at ^{14}C incorporated in genetic material in the chapter on nuclear medicine.^(a)

VI. Summary and Commentary

Some of the earliest inhalation problems anticipated in the days of the Manhattan Engineer District concerned the radioactive noble gases expected to be produced in the fission process. Because these gases move much more freely than particles and are less likely to combine with cell or tissue constituents, there is little tendency for long retention of these substances. Yet, there were a few substantive biomedical problems that required investigation. Most important concerned iodine vapor (plus the compounds formed after the vapor condenses); tritium in its various forms; and to a lesser degree, krypton, xenon, and radioactive carbon dioxide.

Unlike the concentrated attacks on inhaled dusts and particles through organized centers, the work on the respirable gases was more diffuse and on a smaller scale. Experimental work on iodine was concentrated to some extent at Hanford, tritium received major attention at Argonne, Brookhaven, Los Alamos, Savannah River, and the EPA laboratories. The noble gases were looked at especially by laboratories of the U.S. Public Health Service and their EPA-operated successors.

Iodine, as an important constituent of reactor off-gases and of fallout from nuclear weapons tests, is the element in this group that poses the most practical problems (see chapters 11 and 12). With most of the others (even tritium, which can be produced in large quantities) the experimental work has had as much or more scientific interest as practical import. With tritium and ^{14}C , the potential for transmutation effects at the time of radioactive disintegration of a nucleus was especially intriguing. Much research went toward divining whether or not the decay of one of these atoms within the intimate structure of the cell nucleus could produce effects over and above those associated with the radiation dose. The answer was positive for tritium, but only under special circumstances, viz., when the tritium was bound at certain specific positions in nucleic acid precursors. Since such specific binding sites are only occasionally labeled from a tritium pool, the effect is of little significance apropos tritium hazards.

Another intriguing aspect with tritium was its very low energy. Thus, all of the energy is deposited in a small volume. Would this increase the effectiveness per rad? For a while it seemed that it did, and a quality factor of about 1.7 for radiation protection was recommended for low-energy electrons and protons. This would include the tritium beta particle. However, subsequent research

(a) It is tempting in a situation with so many large gaps to inquire peevishly why no one has looked into them. (Perhaps someone has, but not in U.S. work.) It is likely that even if anyone were interested, he would have had trouble getting financial support for work that had such a high risk of being negative and "exactly as predicted."

indicated that this was not a sufficiently constant phenomenon to warrant use in radiation protection. An important practical factor in tritium exposure, however, is its absorption through the unbroken skin, a phenomenon that led to halving the allowable concentrations in ambient media.

Of special interest to basic radiobiology was the multigenerational study of neoplastic and life-span effects of tritium in rats exposed in utero and/or throughout life. On the basis of this work, we cannot dismiss tritium as a totally innocuous agent, even though it is not in the same class as strontium, plutonium, or even iodine.

Radiokrypton and radioxenon were rather exhaustively studied kinetically. The results belied the simple postulate that these gases moved freely about in living organisms. There was evidence of several components in the retention curves and thus of several compartments for their residence. Partition among organs was not uniform, due in part to different fat contents of different tissues.

The work with inhaled ^{14}C was initiated for hazard evaluation. Before long it became of more interest for the knowledge imparted on the pathways followed by inhaled carbon.

References

- Abrams, R. 1943a. *Inhalation experiments*. Metallurgical Laboratory report CH-708, p. 20, June 7, 1943, declassified January 15, 1958.
- Abrams, R. 1943b. *Xenon and argon experiments*. Metallurgical Project monthly report CH-630, p. 9, May 7, 1943, declassified December 4, 1956. Also in section C, biological research by K. S. Cole.
- Adolph, E. F. 1943. *Physiological regulations*. Lancaster, Pa.: The James Cattell Press.
- Agnew, H. M. 1982. Tritium Production. *Science* 215:612-14.
- Alvarez, L. W. and R. Cornog. 1939. Helium and hydrogen of mass 3. *Phys. Rev.* 56:613.
- Anderson, E. C. and W. H. Langham. 1954. *A theoretical consideration of the hazards associated with acute exposure to high concentrations of tritium gas*. LA-1646. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Andrew, F. D., M. R. Sikov, and D. H. Willard. 1977. Disposition of ^{85}Kr in gravid rats. In *Pacific Northwest Laboratory annual report for 1976 to the ERDA Assistant Administrator for Environment and Safety, Part 1 Biomedical Sciences*. BNWL-2100, pt. 1, pp. 80-81. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Andrew, F. D., M. T. Karagianes, M. R. Sikov, J. E. Ballou, D. H. Willard, C. R. Watson, and P. G. Doctor. 1978. Studies in pregnant sheep exposed to krypton-85 atmospheres. In *Pacific Northwest Laboratory annual report for 1977 to the DOE Assistant Secretary for the Environment, Part 1 Biomedical Sciences*. PNL-2500, pt. 1, pp. 3.76-3.77. Richland, Wash.: Pacific Northwest Laboratory.
- Bair, W. J., M. D. Snyder, R. A. Walters, and R. F. Keough. 1963. Effect of I^{127} on thyroid uptake of inhaled I^{131} . *Health Phys.* 9:1399-1410.
- Baker, N., W. W. Shreeve, R. A. Shipley, G. E. Incefy, and M. Miller. 1954. C^{14} studies in carbohydrate metabolism. I. The oxidation of glucose in normal human subjects. *J. Biol. Chem.* 211:575-92.
- Ballou, J. E. 1976. Toxicology of tritium and the noble gases. In *Pacific Northwest Laboratory annual report for 1975 to the ERDA Division of Biomedical and Environmental Research, Part 1 Biomedical Sciences*. BNWL-2000, pt. 1, p. 63. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Ballou, J. E. 1982. Toxicology of krypton-85. In *Pacific Northwest Laboratory annual report for 1981 to the DOE Office of Energy Research, Part 1 Biomedical Sciences*. PNL-4100, pt. 1, pp. 105-6. Richland, Wash.: Pacific Northwest Laboratory.

- Ballou, J. E. and H. S. DeFord. 1981. Effects in newborn rats exposed to ^{85}Kr atmospheres. *Pacific Northwest Laboratory annual report for 1980 to the DOE Assistant Secretary for Environment, Part 1 Biomedical Sciences*. PNL-3700, pt. 1, pp. 138-39. Richland, Wash.: Pacific Northwest Laboratory.
- Bennett, L. R., F. K. Bauer, D. T. Mason, E. Braunwald, W. H. Oldendorf, W. H. Blahd, and D. L. Hutchinson. 1965. Diagnosis of cardiovascular disease. Chapter 14 in *Nuclear medicine*, ed. W. H. Blahd, pp. 410-29. New York: McGraw-Hill.
- Bernard, S. R. 1973. A human metabolic model for ^{14}C -labelled metabolites useful in dose estimation. In *Proceedings of the 3d international congress of the International Radiation Protection Association*, ed. W. S. Snyder, CONF-730907-P2, pp. 1400-1405. Held in Washington, D.C., September 9-14, 1973. Oak Ridge, Tenn.: Technical Information Center.
- Bernard, S. R. and W. S. Snyder. 1975. *Metabolic models for estimation of internal radiation exposure received by human subjects from the inhalation of noble gases*. ORNL-5046. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Blaylock, B. G. and J. R. Trabalka. 1976. Effectiveness of tritium and ^{239}Pu in producing chromosome aberrations in *Chironomus riparius*. In *Biological and environmental effects of low-level radiation*, STI/PUB/409, vol. 2, pp. 45-50. Proceedings of a symposium held in Chicago, November 3-7, 1975. Vienna: International Atomic Energy Agency.
- Book, S. A. 1980. *Relative hazard of radioiodine as a function of (a) radiation quality and (b) age at exposure*. NUREG/CR-1228. Davis, Calif.: Univ. of Calif. at Davis, Laboratory of Energy-Related Health Research.
- Bradley, F. J., R. Blais, and A. Jones. 1971. Impact of tritium on the watch industry, 1966-1970. *Radiol. Health Data Rep.* 12:601-10.
- Brookhaven National Laboratory. 1948. *Symposium on radioiodine*, July 28-30, 1948. BNL-C-5, AECU-51. Upton, N.Y.: Brookhaven National Laboratory.
- Brues, A. M. and D. L. Buchanan. 1948. Studies on the over-all CO_2 metabolism of tissues and of total organisms. In *Biological applications of tracer elements*, vol. 13, pp. 52-62. Proceedings of a symposium on quantitative biology held in Cold Spring Harbor, N.Y. Long Island, N.Y.: The Biological Laboratory.
- Brues, A. M., A. N. Stroud, and L. Reitz. 1952. Toxicity of tritium oxide to mice. *Proc. Soc. Exp. Biol. Med.* 79: 174-76.
- Bruner, H. D. 1963. Symposium on the biology of radioiodine: Statement of the problem. *Health Phys.* 9:1083-89.
- Buchanan, D. L. 1951. Uptake and retention of fixed carbon in adult mice. *J. Gen. Physiol.* 34:737-59.
- Buchanan, D. L. and A. Nakao. 1952. Turnover of bone carbonate. *J. Biol. Chem.* 198:245-57.
- Buchheit, R. G., H. R. Schreiner, and G. F. Doebbler. 1966. Growth responses of *Neurospora crassa* to increased partial pressures of the noble gases and nitrogen. *J. Bacteriol.* 91:622-27.
- Bursian, S. J., D. F. Cahill, J. W. Laskey, and L. N. Parker. 1975. Some aspects of brain neurochemistry after intrauterine exposure to tritium. *Int. J. Radiat. Biol. & Relat. Stud. Phys. Chem. & Med.* 27:455-61.
- Bustad, L. K., ed. 1963. *The biology of radioiodine*. Proceedings of the 2d annual Hanford biology symposium held in Richland, Wash., June 17-19, 1963. *Health Phys.* 9:1081-1426.
- Butler, H. L. 1962. *Observed effective half life of tritium at the Savannah River Plant*. DP-831, pp. 38-45.
- Butler, H. L. and J. H. LeRoy. 1965. Observation of biological half-life of tritium. *Health Phys.* 11:283-85.
- Cahill, D. F. and C. L. Yuile. 1970. Tritium: Some effects of continuous exposure *in utero* on mammalian development. *Radiat. Res.* 44:727-37.
- Cahill, D. F., L. W. Reiter, J. A. Santolucito, B. F. Rehnberg, M. E. Ash, M. J. Favor, S. J. Bursian, J. F. Wright, and J. W. Laskey. 1976. Biological assessment of continuous exposure to tritium and lead in the rat. In *Biological and environmental effects of low-level radiation*, STI/PUB/409, vol. 2, pp. 65-78. Proceedings of a symposium held in Chicago, November 3-7, 1975. Vienna: International Atomic Energy Agency.

- Cahill, D. F., J. F. Wright, J. H. Godbold, J. M. Ward, J. W. Laskey, and E. A. Tompkins. 1975a. Neoplastic and life-span effects of chronic exposure to tritium. I. Effects on adult rats exposed during pregnancy. *J. Natl. Cancer Inst.* 55: 371-74.
- Cahill, D. F., J. F. Wright, J. H. Godbold, J. M. Ward, J. W. Laskey, and E. A. Tompkins. 1975b. Neoplastic and life-span effects of chronic exposure to tritium. II. Rats exposed in utero. *J. Natl. Cancer Inst.* 55:1165-69.
- Carsten, A. L. and S. L. Commerford. 1976. Dominant lethal mutations in mice resulting from chronic tritiated water (HTO) ingestion. *Radiat. Res.* 66:609-14.
- Carsten, A. L. and E. P. Cronkite. 1976. Genetic and hematopoietic effects of long-term tritiated water ingestion in mice. In *Biological and environmental effects of low-level radiation*, STI/PUB/409, vol. 2; pp. 51-56. Proceedings of a symposium held in Chicago, November 3-7, 1975. Vienna: International Atomic Energy Agency.
- Carsten, A. L. and E. P. Cronkite. 1979. Comparison of late effects of single x-ray exposure, chronic tritiated water ingestion and chronic caesium-137 gamma exposure in mice. In *Biological implications of radionuclides released from nuclear industries*, STI/PUB/522, vol. 1, pp. 269-76. Proceedings of a symposium held in Vienna, March 26-30, 1979. Vienna: International Atomic Energy Agency.
- Cohen, J. J. and G. H. Higgins. 1973. The socioeconomic impact of low-level tritium releases to the environment. In Moghissi and Carter 1973, pp. 14-22.
- Cohn, S. H., K. J. Ellis, and H. Susskind. 1979. Evaluation of the health hazard from inhaled krypton-85. In *Biomedical implications of radionuclides released from nuclear industries*, STI/PUB/522, vol. 1, p. 315-28. Proceedings of a symposium held in Vienna, March 26-30, 1979. Vienna: International Atomic Energy Agency.
- Cole, K. S. 1943. Biological research. In Stone 1943, pp. 9-10.
- Cole, K. S. 1944. Xenon-preparation and inhalation. Metallurgical Project report CH-1673, p. 20, declassified March 25, 1952.
- Commerford, S. L., A. L. Carsten, and E. P. Cronkite. 1977. The distribution of tritium in the glycogen, hemoglobin, and chromatin of mice receiving tritium in their drinking water. *Radiat. Res.* 72:333-42.
- Dailey, M., I. Wender, and R. Abrams. 1945. Tracer studies with inhaled eight-day iodine. *Terminal Report on Problem Assignment—244 MLH 2110*. Metallurgical Project report CH-2777, AEC report MDDC-251, January 10, 1945, declassified January 31, 1947.
- Dewey, W. C., R. M. Humphrey, and B. A. Jones. 1965. Comparisons of tritiated thymidine, tritiated water, and cobalt-60 gamma rays in inducing chromosomal aberrations. *Radiat. Res.* 24:214-38.
- Diethorn, W. S. and W. L. Stockho. 1972. The dose to man from atmospheric ⁸⁵Kr. *Health Phys.* 23:653-62.
- Dobson, R. L. 1976. Low level chronic exposure to tritium. An improved basis for hazard evaluation. In *Biological and environmental effects of low-level radiation*, STI/PUB/409, vol. 2, pp. 57-63. Proceedings of a symposium held in Chicago, November 3-7, 1975. Vienna: International Atomic Energy Agency.
- Dobson, R. L. and T. C. Kwan. 1976. The RBE of tritium radiation measured in mouse oocytes: Increase at low exposure levels. *Radiat. Res.* 66:615-25.
- Ellis, K. J., S. H. Cohn, H. Susskind, and H. L. Atkins. 1977. Kinetics of inhaled krypton in man. *Health Phys.* 33:515-22.
- Evans, E. A. 1966 and 1974. *Tritium and its compounds*. 1st ed. 1966, 2d ed. 1974. New York-Toronto: John Wiley & Sons.
- Federal Radiation Council. 1962. *Pathological effects of thyroid irradiation*. Report of a panel of experts from the Committee on the Biological Effects of Atomic Radiation. Washington, D.C.: National Academy of Sciences-National Research Council.
- Feinendegen, L. E. and V. P. Bond. 1973. Transmutation versus beta irradiation in the pathological effects of tritium decay. In Moghissi and Carter 1973, pp. 221-31.
- FRC. See Federal Radiation Council.
- Furchner, J. E. 1957. Relative biological effectiveness of tritium beta-particles and Co⁶⁰ gamma-rays measured by lethality in CF1 mice. *Radiat. Res.* 6:483-90.
- Getzendaner, M. E., M. P. Fujihara, and H. A. Kornberg. 1953. Determination of RBE by microbiological methods. In *Biology research annual report for 1952*, HW-28636, pp. 98-109. Richland, Wash.: Hanford Works.

- Hall, E. J., R. Oliver and J. S. Bedford. 1967. The relative biological effectiveness of tritium beta particles compared to gamma radiation: Its dependence on dose-rate. *J. Radiol.* 40:704-10.
- Hamilton, J. G. 1943a. A letter from J. G. Hamilton to C. W. Cooper, July 27, 1943. Report MUC-HG #200 declassified November 1966.
- Hamilton, J. G. 1943b. In Stone 1943, p. 4.
- Hamilton, J. G. 1944. *Summary of iodine physiology and metabolic studies using radioactive isotopes of iodine*. Metallurgical Project report CH-2257, October 18, 1944, declassified June 25, 1947.
- Hamilton, J. G. 1947. *Radioactive xenon (Xe^{127})-tracer studies*. Chapter 12 in Metallurgical Project declassified report MDDC-1275, declassified 1947.
- Hatch, F. T. and J. A. Mazrimas. 1971. *Tritiation of animals from tritiated water*. UCRL-73154, rev. 1. Berkeley, Calif.: Univ. of Calif., Lawrence Livermore Radiation Laboratory.
- Health Physics Society. 1971. *Health physics aspects of nuclear facility siting*. Proceedings of the 5th annual Health Physics Society midyear topical symposium, held in Idaho Falls, November 3-6, 1970. Eastern Idaho Chapter of Health Physics Society. [Three volumes.]
- Hellman, L., W. Peacock, M. Edinoff, R. Rosenfeld, T. Gallagher, and Dobriner. 1953. The metabolic fate of radioactive carbon labeled glycine and acetate in humans. In *Proceedings of the Isotopes Techniques Conference*, H. M. Stationery Office, p. 229.
- Hendrickson, M. M. 1970. *The dose from ^{85}Kr released to the earth's atmosphere*. BNWL-SA-3233A. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Holland, J. Z. 1963. Physical origin and dispersion of radioiodine. *Health Phys.* 9: 1095-1103.
- Houšková, M., A. Čajková, E. Kunz, and L. Náměstek. 1973. Excretion of tritium in workers preparing labeled compounds. In *Proceedings of the 3d international congress of the International Radiation Protection Association*, ed. W. S. Snyder, CONF-730907-P1, pp. 538-43. Held in Washington, D.C., September 9-14, 1973. Oak Ridge, Tenn.: Technical Information Center.
- HPS. See Health Physics Society.
- IAEA. See International Atomic Energy Agency.
- ICRP. See International Commission on Radiological Protection.
- International Atomic Energy Agency. 1962. *Tritium in the physical and biological sciences*. Proceedings of a symposium held in Vienna, May 3-10, 1961. [Two volumes.] Vienna: International Atomic Energy Agency.
- International Atomic Energy Agency. 1979. *Behavior of tritium in the environment*, STI/PUB/498, pp. 7-11. Proceedings of a symposium held in San Francisco, October 1978. Vienna: International Atomic Energy Agency.
- International Commission on Radiological Protection. 1959. *Report of Committee II on permissible dose for internal radiation*. International Commission on Radiological Protection, publ. 2. New York-London: Pergamon Press.
- International Commission on Radiological Protection. 1966. *Recommendations of the ICRP* publ. 9 (adopted September 17, 1965). Oxford: Pergamon Press.
- Jacobs, D. G. 1968. *Sources of tritium and its behavior upon release to the environment*. AEC Critical Review Series. Oak Ridge, Tenn.: U.S. Atomic Energy Commission.
- Jennings, F. L. and A. M. Brues. 1951. *Toxicity of tritium oxide on continued administration in rats*. ANL-4625, p. 229. Argonne, Ill.: Argonne National Laboratory.
- Johnson, H. A. 1973. The quality factor for tritium radiation. In Moghissi and Carter 1973, pp. 231-39.
- Kaufman, S. L., M. L. Colvin, R. Lieberman, A. A. Moghissi, B. F. Rehnberg, and R. C. McMillan. 1971. *Investigation of tritiated luminous compounds*. EERL 71-2. Washington, D.C.: U.S. Environmental Protection Agency.
- Kirk, W. P. 1972. *^{85}Kr : A review of the literature and an analysis of radiation hazards*. Report NP-19251. Rockville, Md.: U.S. Environmental Protection Agency.

- Kirk, W. P. and D. A. Morken. 1975. *In vivo* kinetic behavior and whole-body partition coefficients of ^{85}Kr in guinea pigs. *Health Phys.* 28:263-73.
- Kirk, W. P., B. F. Rehnberg, and D. A. Morken. 1975. Acute lethality in guinea pigs following respiratory exposure to ^{85}Kr . *Health Phys.* 28:275-84.
- Kornberg, H. A. 1982a. Personal communication.
- Kornberg, H. A. 1982b. Taped personal interview in Vancouver, Wash.
- Krejčí, K. and A. Zeller, Jr. 1979. Tritium pollution in the Swiss luminous compound industry. In *Behavior of tritium in the environment*, STI/PUB/498, pp. 65-77. Proceedings of a symposium held in San Francisco, October 16-20, 1978. Vienna: International Atomic Energy Agency.
- Lambert, B. E. 1969. Cytological damage produced in the mouse testes by tritiated thymidine, tritiated water and x-rays. *Health Phys.* 17:547-57.
- Laskey, J. W., J. L. Parrish, and D. F. Cahill. 1973. Some effects of lifetime parental exposure to low levels of tritium in the F_2 generation. *Radiat. Res.* 56:171-79.
- Lassen, N. A. 1964. Assessment of tissue radiation dose in clinical use of radioactive inert gases, with examples of absorbed doses from $^3\text{H}_2$, ^{85}Kr and ^{133}Xe . *Minerva Nucl.* 8:211-17.
- Libby, W. F. 1955. *Radiocarbon dating*, 2d ed. Chicago: Univ. of Chicago Press.
- Libby, W. F. 1973. History of tritium. In Moghissi and Carter 1973, pp. 3-11.
- Markoe, A. M., R. Anigstein, and R. J. Schulz. 1970. Effects of inert gases and nitrous oxide on the radiation sensitivity of HeLa cells. *Phys. Med. Biol.* 15:200.
- Mason, A. S. and H. G. Östlund. 1979. Atmospheric HT and HTO: V Distribution and large-scale circulation. In *Behavior of tritium in the environment*, STI/PUB/498, pp. 3-16. Proceedings of a symposium held in San Francisco, October 16-20, 1978. Vienna: International Atomic Energy Agency.
- Moghissi, A. A. and M. W. Carter, eds. 1973. *Tritium*, CONF-710809. Proceedings of a symposium held in Las Vegas, Nevada, August 28-September 3, 1971. Phoenix-Las Vegas: Messenger Graphics.
- Moghissi, A. A. and M. W. Carter. 1975. *Public health implications of radioluminous materials*. DHEW publ. (FDA) 76-8001. Washington, D.C.: Bureau of Radiological Health, U.S. Food and Drug Administration.
- Moskalev, Yu. I. 1966. *Distribution and biological effects of radioactive isotopes*. AEC-tr-6944, original publication by Atomizdat, Moscow, 1966.
- Moskalev, Yu. I. 1968. *Tritium oxide*. AEC-tr-7298, original publication by Atomizdat, Moscow, 1968.
- National Council on Radiation Protection and Measurements. 1971. *Basic radiation protection criteria*. Report no. 39. Bethesda, Md.
- National Council on Radiation Protection and Measurements. 1977. *Protection of the thyroid gland in the event of releases of radioiodine*. Report no. 55. Washington, D.C.
- National Council on Radiation Protection and Measurements. 1979. *Tritium in the environment*. Report no. 62. Washington, D.C. [See also summary in IAEA 1979.]
- National Council on Radiation Protection and Measurements. 1985. *Carbon-14 in the environment*. Report no. 81. Bethesda, Md.
- NCRP. See National Council on Radiation Protection and Measurements.
- NRC. See Nuclear Regulatory Commission.
- Nuclear Regulatory Commission. 1975. *Reactor safety study: An assessment of accident risks in U.S. commercial nuclear power plants*. WASH-1400, NUREG-75/014, "The Rasmussen Study." Washington, D.C.
- Nussbaum, E. and J. B. Hursh. 1957. Radon solubility in rat tissues. *Science* 125:552-53.
- Oak Ridge National Laboratory. 1965. *International symposium on fission product release and transport under accident conditions*, CONF-650407. Held in Oak Ridge, Tenn., April 5-7, 1965. [Two volumes.]
- ORNL. See Oak Ridge National Laboratory.
- Osborne, R. V. 1979. Diffusion kinetics of tritiated water through human skin. In *Behavior of tritium in the environment*, STI/PUB/498, pp. 509-20. Proceedings of a symposium held in San Francisco, October 16-20, 1978. Vienna: International Atomic Energy Agency.

- Pinson, E. A. 1952. Water exchanges and barriers as studied by the use of hydrogen isotopes. *Physiol. Rev.* 32:123-34.
- Pinson, E. A. and W. H. Langham. 1957. Physiology and toxicology of tritium in man. *J. Appl. Physiol.* 10:108-26. Reprinted as a landmark paper in *Health Phys.* 38:1087-1110.
- Richmond, C. R., J. E. Furchner, and W. H. Langham. 1960. *Estimation of maximum permissible concentrations of radioisotopes in water (MPC)_w from interspecies correlations. I. Comparison of estimated and measured values for zinc-65 and tritium.* Semiannual report of H-4 group, July-December 1960, pp. 25-33. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory, Health Division.
- Richmond, C. R., W. H. Langham, and T. T. Trujillo. 1962. Comparative metabolism of tritiated water by mammals. *J. Cell Comp. Physiol.* 59:45-53.
- Russell, W. L., R. B. Cumming, E. M. Kelly, and E. L. Phipps. 1979. Induction of specific-locus mutations in the mouse by tritiated water. In *Behavior of tritium in the environment*, STI/PUB/498, pp. 489-97. Proceedings of a symposium held in San Francisco, October 16-20, 1978. Vienna: International Atomic Energy Agency.
- Sanders, S. M., Jr. and W. C. Reinig. 1968. Assessment of tritium in man. In *Diagnosis and treatment of deposited radionuclides*, pp. 534-42. Proceedings of a symposium held in Richland, Wash., May 15-17, 1967. Amsterdam: Excerpta Medica Foundation.
- Seelentag, W. 1973. Two cases of tritium fatality. In Moghissi and Carter 1973, pp. 267-80.
- Silini, G., P. Metalli, and G. Vulpis. 1973. Radiotoxicity of tritium in mammals. *Critical analysis of the extrapolation to man of the results of tritium incorporation into animal tissues*, CNEN Report, EUR 5033e. Rome: Commission of the European Communities.
- Siri, W. and J. Evers. 1962. Tritium exchange in biological systems. In *Tritium in the physical and biological sciences*, vol. 2, pp. 71-84. Proceedings of a symposium held in Vienna, May 3-10, 1961. Vienna: International Atomic Energy Agency.
- Slatkin, D. N., A. L. Carsten, S. L. Commerford, K. W. Jones, and H. W. Kramer. 1979. Genetic hazard of ^3H : Estimation by oocyte uptake of ^3H . In *Biological implications of radionuclides released from nuclear industries*, STI/PUB/522, vol. 1, pp. 231-40. Proceedings of a symposium held in Vienna, March 26-30, 1979. Vienna: International Atomic Energy Agency.
- Snyder, W. S., B. R. Fish, S. R. Bernard, M. R. Ford, and J. R. Muir. 1968. Urinary excretion of tritium following exposure of man to HTO—A two exponential model. *Phys. Med. Biol.* 13:547-59.
- Spalding, J. F., W. Langham, and E. C. Anderson. 1956. The relative biological effectiveness of tritium β -radiation with the broad bean root (*Vicia faba*) as a test system. *Radiat. Res.* 4:221-27.
- Stone, R. S. 1943. Metallurgical Project monthly report, CH-459. February 9, 1943, declassified March 12, 1952.
- Storer, J. B., P. S. Harris, J. E. Furchner, and W. H. Langham [in a group of twenty investigators]. 1957. The relative biological effectiveness of various ionizing radiations in mammalian systems. *Radiat. Res.* 6:188-288.
- Susskind, H., H. L. Atkins, S. H. Cohn, K. J. Ellis, and P. Richards. 1977. Whole-body retention of radioxenon. *J. Nucl. Med.* 18:462-71.
- Thomas, R. L., J. K. Scott, and T. L. Chiffelle. 1970. Metabolism and toxicity of inhaled and injected ^{131}I in the rat. *Am. Ind. Hyg. Assoc. J.* 31:213-20.
- Tobias, C. A., H. B. Jones, J. H. Lawrence, and J. G. Hamilton. 1949. The uptake and elimination of krypton and other inert gases by the human body. *J. Clin. Invest.* 28:1375-85.
- Unruh, C. M. 1970a. *Nuclear power as a source of contamination on a global scale.* BNWL-SA-3665. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Unruh, C. M. 1970b. *Present and projected sources of environmental radiation (the givens).* Paper presented at a meeting of the Health Physics Society, June 18-July 2, 1970. BNWL-SA-3354. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Vennart, J. 1968. The quality factor for low-energy β -emitters. *Health Phys.* 14:541-48.
- Wagner, H. N., Jr. 1965. Measurement and diagnosis of pulmonary function and disease. In *Nuclear medicine*, ed. W. H. Bland, chapter 15, pp. 439-59. New York: McGraw-Hill.

- Wawerna, J. C. 1973. Biological implications of the application of tritiated luminous compounds. In Moghissi and Carter 1973, pp. 356-63.
- Wehmann, G. 1963. Comparison of ingestion to inhalation dose to man from I^{131} . *Health Phys.* 9:1221-22.
- Whipple, G. H. 1969. Approaches to the calculation of limitations of nuclear detonations for peaceful purposes. In *Public health aspects of nuclear explosives*, SWRHL82, CPEHS, ECA, BRH, pp. 694-96. Proceedings of a symposium held in Las Vegas, April 7-19, 1969. Las Vegas, Nev.: Southwest Radiological Health Laboratory.
- Whitton, J. T. 1968. *Dose arising from inhalation of noble gases*. RB/D/N-1274. Berkeley: U.K. Central Electricity Generating Board.
- Willard, D. H. and J. E. Ballou. 1977a. Accumulation and distribution of ^{85}Kr in rats exposed to ^{85}Kr atmospheres. In *Pacific Northwest Laboratory annual report for 1976 to the ERDA Assistant Administrator for Environment and Safety, Part 1 Biomedical Sciences*. BNWL-2100, pt. 1, pp. 73-77. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Willard, D. H. and J. E. Ballou. 1977b. Retention of ^{85}Kr in the rat and beagle dog. In *Pacific Northwest Laboratory annual report for 1976 to the ERDA Assistant Administrator for Environment and Safety, Part 1 Biomedical Sciences*. BNWL-2100, pt. 1, pp. 78-79. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Willard, D. H., H. D. Tolley, and J. E. Ballou. 1981. Effects of chronic ^{85}Kr exposure in rats. *Pacific Northwest Laboratory annual report for 1980 to the DOE Assistant Secretary for Environment, Part 1 Biomedical Sciences*. PNL-3700, pt. 1, pp. 136-37. Richland, Wash.: Pacific Northwest Laboratory.
- Willard, D. H., J. E. Ballou, H. A. Ragan, and A. J. Gandolfi. 1978. Disposition and biological effect of inhaled ^{85}Kr . In *Pacific Northwest Laboratory annual report for 1977 to the DOE Assistant Secretary for Environment, Part 1 Biomedical Sciences*. PNL-2500, pt. 1, pp. 3.73-3.75. Richland, Wash.: Pacific Northwest Laboratory.
- Willard, D. H., H. S. DeFord, R. E. Gerk, and J. E. Ballou. 1979. Effect of chronic ^{85}Kr exposure. In *Pacific Northwest Laboratory annual report for 1978 to the DOE Assistant Secretary for Environment, Part 1 Biomedical Sciences*. PNL-2850, pt. 1, pp. 3.61-3.62. Richland, Wash.: Pacific Northwest Laboratory.
- Wollan, E. O. and R. J. Stephenson. 1942. *5.4 day xenon as a radioactive hazard connected with the operation of the pilot plant and with chemical processing of the products*. Metallurgical Project report CH-259, pp. 2-3, September 15, 1942, declassified February 10, 1958.
- Woodard, H. Q. 1970. *The biological effects of tritium*. HASL-229. pp. 49. Washington, D.C.: U.S. Atomic Energy Commission, Health and Safety Laboratory.
- Worman, F. C. V., D. Turney, and V. Lotz. 1954. The relative biological effectiveness of tritium beta rays in producing splenic and thymic weight loss in mice. LA-1641. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Wylie, K. F., W. A. Bigler, and G. R. Grove. 1963. Biological half-life of tritium. *Health Phys.* 9:911-14.
- Zirkle, R. E. 1943. *The radiobiological importance of specific ionization*. Metallurgical Laboratory report CH-946, September 21, 1943, declassified as AEC report MDDC-444.

Preface to Section IV Environment Chapters

No book purporting to review the history of radioactivity and health would be complete without a discussion of the environmental aspects of the subject. Yet, consideration of these to the extent attempted for the more strictly laboratory research work taken up in other sections is impossible without greatly exceeding all reasonable restraints on the length of this work. While they were slow to start, environmental considerations now occupy enormous segments of the literature, and they continue to grow. Thus, the chapters in this section will constitute a change of pace from those that have preceded and those to follow. We will concentrate on the genesis of the major lines of investigation, give details where necessary and desirable; but make no attempt to provide documentation of the original literature to the extent attempted in many other sections. Fortunately, the field is so very active that current and excellent book-length reviews are readily available to the interested reader. Hence, much of the referencing will be to these, except for the earlier days.

Some facets of environmental exposures to radioactivity have already been discussed, including radium and radon in mines, spas, and drinking water (chapters 1 and 3); noble gases and volatile radionuclides as part of the review of respirable gases and particles (chapters 9 and 10). Others will appear in connection with the setting of standards (chapter 16). However, the research and problems considered therein were geared primarily to occupational exposure problems, although a few involved population exposures to a minor degree. By contrast, the focus and *raison d'être* for most of the work to be described in the chapters of this section are potential exposure of population groups, ranging from those around nuclear energy plant operations to all of mankind in the consideration of global fallout.

The work began with investigations oriented toward both worker and population exposures around nuclear production sites (chapter 11). It reached its full flowering in the events and research associated with fallout from nuclear weapons tests. Indeed, this new dimension changed the world as we knew it and continues to expand far beyond purely technical and scientific matters. Chapter 12 will review primarily the biomedical problems and findings coming from field studies on fallout, while chapter 13 will take up laboratory research stimulated by the problems identified in the field work. This research is closely related to some already reviewed, particularly in chapters 8, 9, and 10, but we

choose to discuss it in this section because of its extreme pertinence to environmental considerations and exposures of not only the human population but of all the biosphere.

Several projects were developed to study specific problems relating to potential environmental contamination on a more limited scale than the fallout from weapons tests. Many of these were designated "safety shots." Other projects involved purposeful dispersion of radionuclides in manners unrelated to weapons tests. They form a somewhat miscellaneous group that does not fit into other chapters. Yet, the results had important bearings on many environmental considerations. For these reasons, and perhaps because this author was personally involved with one of the projects, the work is drawn together separately as chapter 14.

The environment section closes with a brief review of how the research and field studies bear on our knowledge of environmental transport systems (chapter 15). This has become a highly sophisticated and complex field, which influences all of ecology, not just the phenomena concerned with radionuclides. Indeed, in many instances the radionuclides are more tools than ends in themselves. We can afford only a brief glimpse of this enormous field. Emphasis will be placed on the earlier work. The reader will be led to the more recent, more complex aspects, largely by references to current reviews.

It may occur to many that much of ecological science, as we know it today, developed from the research and field studies described or referenced in the chapters of this section. It would be presumptuous to conclude that it could not have happened through other avenues. Ecology is a very broad field. Only some aspects were materially changed by the work to be described. Nevertheless, there can be no doubt that some areas were very materially advanced and much sooner than they would otherwise have been. Nor can there be any doubt that ecology as a field was transformed from a quiet, somewhat academic subject into the limelight of both scientific and public concerns. The investigations reviewed in the chapters in this section should supply ample documentation for these conclusions.

In these chapters, we will have much to say about the field of radioecology. For orientation, the following quotations from a recent book by Whicker and Schultz (1982, see chapter 11) is presented:

"Radioecology" or "radiation ecology" can be considered a field of endeavor which encompasses the relationships between ionizing radiation or radioactive substances and the environment, or subunits within the environment. These subunits may be populations, communities, ecosystems, biomes, or even the biosphere. Radiobiology, in contrast, deals with radiation and levels of biological organization from the molecule to the organism. The primary subdivisions of radiation ecology include:

1. Radionuclide movement within ecological systems and accumulation within specific ecosystem components such as soil, air, water, and biota
2. Ionizing radiation effects on individual species, populations, communities, and ecosystems
3. Use of radionuclides and ionizing radiation in studies of structure and function of ecosystems and their component subsystems.

Questions commonly asked regarding movement, accumulation, and effects of radionuclides in ecological systems include:

1. How rapidly do radionuclides move from one part of the system to another and what are the mechanisms and pathways of such transfers?

2. What are the relative concentrations and radiation doses from radionuclides in important biological components relative to the total amount of environmental contamination?
3. What is the long-term behavior and ecological effect of radionuclides in the environment?
4. At what environmental concentrations are effects, if any, seen in populations?
5. Environmental studies using radioisotopic tracers may answer such questions as: Where do animals move? What do they eat? How much and which elements and nutrients are used? What are the dynamics of upper-lower atmospheric mixing? What are the circulation patterns of lakes and oceans?

Behavior of radionuclides in the environment is governed by a highly complex set of natural processes and circumstances. Nearly every component of an ecological system will have some influence upon the fate of radioactive materials introduced into the system. Of major significance, however, is the fact that natural processes may concentrate radionuclides in biological tissues to levels that are orders of magnitude higher than in the ambient media of air and water. Further, there is no doubt that radionuclides, in sufficient concentrations, are harmful to all living systems.

The authors believe that radioecology is an important, complex, and diverse science, dictating an interdisciplinary approach, which is accomplished in practice by the varied and unique academic training of radioecologists. The field draws heavily on information from the basic physical and biological sciences, and current curricula of the radioecologist may encompass physics, chemistry, mathematics, geology, plant and animal ecology and physiology, taxonomy, radiation biology, dosimetry, and more. Because radioecology integrates these fields, to some extent, it frequently leads to interdisciplinary contributions which can aid the extension of each discipline.

The work reviewed in these chapters has extensive ramifications for all problems of environmental contamination. As we stated in the inhalation toxicology section, it was the work directed toward radionuclides and radiation biology that led the way to a considerable extent.

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OUTLINE

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Capsule Chronology

- April 1943** Ground broken for Hanford reactors.
- May 1943** Stafford Warren initiates activities for radiobiological studies of fisheries and ecological investigations of Columbia River.
- August 1943** First contract let between University of Washington (Applied Fisheries Laboratory) and OSRD^(a) (Donaldson et al.).
- 1943** Clinton reactor goes into operation at Oak Ridge, soon followed by other facilities of MED. Routine industrial hygiene and some environmental sampling, but no organized ecological program.
- 1945** Formal ecology program set up at Hanford in Quonset hut (Foster et al.). Pile effluents studied.
- 1946** Work begins on Columbia River itself. Joint Hanford–University of Washington operation.
- 1949** Concluded that Hanford reactors do not threaten fisheries resources or water supplies of Pacific Northwest, but work produces many surprises. Columbia River Advisory Group formed.
- 1950** Ecology program established at Oak Ridge, primarily around environmental contamination in and around White Oak Lake. Joint TVA–ORNL program (Krumholz et al., Struxness).
USPHS sends ecology team to join in Hanford work.
Term “radioecology” begins to be used.
- Early 1950s** Ecological work further broadened at Hanford. Terrestrial ecology program added.
Morgan and Struxness push for financing of Oak Ridge program.
Clinch River comes under study.
- 1950s** Development of ecological facets of operations at National Reactor Testing Station (Idaho Falls).
- 1951** Initial ecology studies at Savannah River site and of Savannah River (Odum at University of Georgia and Philadelphia Academy of Natural Sciences, respectively).
- 1952** Descriptions of Canadian ecological work around Chalk River Plant (Langford and Rigler).
- 1954** Start-up of Rocky Flats plant (Colorado) accompanied by environmental surveys.
- 1955** Stanley Auerbach joins Oak Ridge group.
Hanford work summarized at first Atoms for Peace Conference (Foster and Davis; Hanson and Kornberg; Parker).
Savannah River–University of Georgia collaborative work described at same conference (Odum).
- 1956** Analyses of doses from “cloud passage” (Holland; Snyder; Parker and Healy; Manley and Fry) given at first Atoms for Peace Conference.

(a) For abbreviations and acronyms, see Appendix D.

- 1956–1958** U.K. studies of Irish Sea off Windscale (Dunster). Priority of liverbread pathway established. Mobile laboratories used for terrestrial surveys around Windscale (Fair and McLean).
- 1957** NAS–NRC report on effects of atomic radiation on oceanography and fisheries.
Review of radioactivity in aquatic forms (Donaldson and Foster).
- October 1957** Windscale incident in U.K. Large amount of follow-up work.
- 1957, 1959** Brookhaven report on consequences of major reactor mishap. Report issued 1957 as WASH-740. Derived paper published 1959 in proceedings of second Atoms for Peace Conference (Kuper and Cowan).
- 1958** Healy et al. (Hanford) discuss routine radiation exposures in environs of a major atomic energy plant. Also wind dispersal of contaminants (Healy and Fuquay). Published 1959 in proceedings of second Atoms for Peace Conference.
Environmental Sciences Branch developed within AEC's Division of Biology and Medicine.
- 1959** Uranium mill tailings surveys enter Congressional hearings, e.g., Animas River in Colorado–New Mexico (work by Tsivoglou and others).
- 1960** Symposium on Radioisotopes in the Biosphere at University of Minnesota (Caldecott and Snyder, eds.). Cogent papers by Bustad, Hanson, Kornberg, Foster, Davis.
- 1960–1979** Fourteen IAEA symposia and seminars bearing on radioecology (listed in text).
- 1960s et seq.** Puerto Rico Nuclear Center studies marine ecology of radionuclides.
Woods Hole Oceanographic Institution enters field.
Scripps Institution of Oceanography mounts several projects at sea and in the laboratory.
USPHS involved to growing extent in terrestrial radioecology.
Ecosystem experiments (in contrast to surveys) begin.
Lawrence Livermore Laboratory joins the field.
Broad program of studies of high radiation background areas of Brazil and India (Eisenbud, NYU).
- 1961** First National Symposium on Radioecology, Colorado State University (Schultz and Klement, eds.).
- 1962** Permanent ecological facility and full-time staff developed at Savannah River.
Ringold Farms study begins at Hanford. Whole-body counting of population.
- 1963** Neal Hines's book *Proving Ground* published. First part reviews the ecological work at Hanford site and Columbia River.
First edition of M. Eisenbud's book *Environmental Radioactivity*.
Work reported from Chalk River, Canada (Ophel).
- 1964** NYU begins work on Hudson River estuary, especially in reference to Indian Point Power Plant (Wrenn, Jinks, Eisenbud).

- 1965** Hanford biology symposium on radiation and terrestrial ecosystems (Hungate, ed.).
- 1966** Stockholm symposium on radioecological concentration processes (Åberg and Hungate, eds.).
Polikarpov's book on aquatic radioecology (USSR); reviews a large amount of work including that in USSR and eastern Europe.
- 1967** Second National Symposium on Radioecology, Ann Arbor, Michigan (Nelson and Evans, eds.).
Publication of Clinch River study (Struxness et al., Oak Ridge).
- Late 1960s** Hanford produces master plan for radioecological research. Marine laboratory opened at Sequim, Washington.
- 1969 et seq.** USPHS work on tritium from nuclear power facilities.
- 1970** University of Minnesota symposium "Nuclear Power and the Public" has many environmental considerations (Foreman, ed.).
Colorado Committee for Environmental Information formed to follow up Rocky Flats contamination (Martell et al.). Reports extended throughout the 1970s.
Health Physics Society symposium on the siting of nuclear facilities (Idaho Falls).
Los Alamos designates a formal environmental studies group. Work divided between local sources of contamination and global fallout (more in chapter 12).
- 1970 et seq.** HASL deeply involved in Rocky Flats measurements and polemic (Krey, Hardy, et al.)
Argonne National Laboratory work on plutonium in the Great Lakes.
- 1971** Third National Radioecology Symposium, Oak Ridge (Nelson, ed.).
Symposium on environmental plutonium at Los Alamos.
Hanford symposium on transuranics includes much work on the environment; published in 1972.
- 1972** Bibliographic review of radioecology by Schultz and Whicker.
Studies of oysters in Pacific Northwest indicate contamination with radionuclides, but no demonstrable effects (Nelson et al.).
Book by Pruter and Alverson on Columbia River estuary published.
- 1973** Book, *Tritium*, edited by Moghissi and Carter, includes much work on environmental aspects.
WASH-1209 and WASH-1250, "The Year 2000," study published.
WASH-1258 environmental statement for light-water-cooled nuclear power reactors published.
Draft environmental impact statement for LMFBR published.
Review of published work on plutonium in the environment by Stannard.
Lawrence Livermore work begins on tritium in aquatic systems.
- 1974** WASH-1535 environmental impact statement for LMFBR.

- 1974 American Nuclear Society symposium on environmental levels of transuranium elements.
- 1975 WASH-1400 reactor safety study.
Fourth National Symposium on Radioecology, Oregon State University (Cushing et al., eds.).
- 1976 Rochester Conference on Environmental Toxicity of Aquatic Radionuclides (Miller, Stannard, eds.); contains suggestions by Foster (Battelle) and Goldberg (Scripps) on how to advance studies of effects in ecosystems.
Hanford group (Battelle) enters the Rocky Flats controversy and makes measurements.
- 1978 Oak Ridge Environmental Sciences Division moves into large new facility.
- 1979 Three Mile Island accident.
Reports of Hanford (Battelle) surveys of school children in Richland; partly regarding site-specific contamination, partly regarding fallout (Harr, Honstead, Soldat).
Discussions of possible ecocycle effects of radionuclides (Donaldson, Foster, Seymour, Auerbach, Larson, Welanders, Bonham).
NCRP report on tritium in the environment.
IAEA symposium on behavior of tritium in the environment.
Studies on tritium from consumer products (NRC, FDA).
Epidemiology survey recommended for Rocky Flats area. Evaluated by Lovelace and HASL workers.
- 1980 Hanson's book on transuranium elements in the environment published.
NEA reports on tritium in the environment.
Continued reports on limnological and radiological parameters in ponds and streams on Hanford site.
- 1981 Further discussion of possible ecocycle effects by Whicker and Schultz.
Sophisticated further analysis of Columbia River system.
- 1982 Two-volume book by Whicker and Schultz, entitled, *Radioecology: Nuclear Energy and the Environment* published.
Harvard epidemiologists look at Rocky Flats data.
More discussion of chronic irradiation effects on populations (Whicker and Schultz).
- 1986 Chernobyl accident.

Chapter 11

Survey of Radioecology: Environmental Studies Around Production Sites

Overview

This first chapter of these five devoted specifically to radionuclides in the environment presents both a brief survey of the field of radioecology and selected aspects of work directed primarily at the production sites. It is historically oriented, of course, and focuses attention on the earlier phases of development of the field. Nevertheless, it is possible, with the help of some excellent recent summaries, to give a reasonable, if capsulized, picture of the field in the early 1980s.

The chapter begins with the development during World War II of radiobiological research on aquatic life forms at the University of Washington Applied Fisheries Laboratory in Seattle and the exhaustive research on the Columbia River and its fisheries done by staff at both the University of Washington and the Hanford Works—all apropos the possible releases of radioactivity from the plutonium production reactors at Hanford. This was the beginning of radioecology. It was the only substantive work in the field during most of World War II.

Under the heading "The Early Postwar Years," the chapter examines the radioecological work in the years 1949 to approximately the mid-1960s. This includes the continuation and expansion of the work on the Columbia River and terrestrial studies at Hanford; the development of the White Oak Lake bed, Clinch River, and other studies at Oak Ridge; and a short review of the environmental studies at and around the Savannah River Plant. After considering these three major production sites, the chapter turns to descriptions of the problems and studies around uranium mill and refinery sites, reactor sites, fuel reprocessing sites, and the work of other U.S. government laboratories and universities. There is a brief review of some of the work done in Canada and the USSR and a fairly detailed description of U.K. activities, especially those around Windscale.

A special section is devoted to tracing the growth and maturation of the field of radioecology, both in the United States and abroad. This is done primarily by reviewing the major U.S. symposia on radioecology, the numerous international seminars and symposia sponsored by the International Atomic Energy Agency

and its collaborator organizations, and more current reviews and books. It is concluded that radioecology has indeed "come of age."

In a section labeled "The Later Years Around the Production Sites," many of the more recent extensions of work at the laboratories discussed earlier are described, plus short reviews of many of the newer entries into the field. This is organized partly around sites where problems arose and partly around the laboratories hosting the work. Here the opportunity is taken to make generalizations where possible and appropriate.

The last major section brings together a miscellaneous group of environmental subjects that required some exposition either as part of the general survey of the field or to introduce still other site-oriented topics. This section includes discussion of the Liquid Metal Fast Breeder Reactor Program and a little more about nuclear power reactors. It discusses the role of the environmental impact statement in furthering the field. It also gives very broad general discussions of marine radioecology, transuranics in the environment, and tritium in the environment. In each case, much of the information is transmitted by citing the contents of important symposia and other publications.

The chapter closes with a short commentary on the material presented.

To aid the reader in following the development of the field and in finding further details, the contents of several of the major symposia and other publications are placed as "notes" at the end of the reference section. Also, the chapter quotes rather liberally from sources that have produced useful and moderately comprehensive generalizations.

I. Introduction

In order to discuss work done around the sites, we will need to introduce some general aspects of radioecology as we go. For this reason, the chapter is labeled as a "survey" as well as a discussion of environmental studies around production sites.

Concern for the possible results of contamination of the environment around sites connected with nuclear energy activities arose very early in the operations. During the years of the Manhattan Engineer District (MED), much of the work was perforce confined to environmental measurements of releases using prevailing industrial hygiene approaches. The MED plants were, in general, too busy with new tasks to give more than average attention to potential environmental problems. They were probably as good neighbors as most industrial plants, but the practices we now take for granted were still to be developed, much less applied to the environment. An outstanding exception to this was the Hanford operation, as we will see in the next section.

The end of World War II and the lifting of security restrictions brought a rising tide of both investigational and surveillance-type work directed at the environments surrounding the production sites in operation, and the planned new facilities. Gradually the work became less oriented toward the particular site and took on an identity of its own as bona fide research with broad objectives. Some installations became centers for the new field of "radioecology" and continue to be so. Environmental concerns played an ever increasing role in all phases of the enterprise so that now they are paramount.

We will emphasize the genesis of the work and the shaping of its primary investigational lines and let the excellent reviews, symposia, and books fill in the details, especially for more recently developed aspects.

II. The Years of World War II: Hanford and Seattle

When it was decided to place the huge production reactors on the Columbia River at the Hanford site, questions arose immediately about their possible environmental impact. After all, the Columbia and its tributaries supplied drinking water for hundreds of communities. Moreover, the fisheries industries of the Pacific Northwest supplied food for millions of people and were a natural resource of first-order importance.

Stafford Warren, the indomitable medical director of the Manhattan Engineer District raised questions about the impact of the Plutonium Project on the Columbia River only a few months after the decision was made to locate the production reactors on its banks. Ground was broken for Hanford on April 6, 1943. Pile construction began on June 7, 1943. On May 20, 1943, Warren started activities aimed toward the broad biomedical and ecological problems.^(a)

It was realized that very little was known about the radiosensitivity of aquatic forms of life. It was suspected that even if adult forms were not more sensitive than terrestrial forms at the same level of phylogenetic development, the possible sensitivity of developing eggs and embryos might be critical to the entire life cycle of salmon and trout, as well as other aquatic forms. Importantly, the spawning and breeding grounds of these species were all along the shores and embayments of the Columbia River; some of them hard by or closely downstream from the reactor sites. Knowledge of the radiosensitivity of all stages of their development was essential.

Neal Hines (1962) tells of the fortunate presence and willingness to serve of Lauren Donaldson at the Applied Fisheries Laboratory of the University of Washington in Seattle and the recruitment of Richard F. Foster, who had just completed a Ph.D. thesis on the effects of ionizing radiation on rainbow trout, and of Arthur Welander who had done likewise with chinook salmon. These, plus Kelshaw Bonham and somewhat later Allyn H. Seymour, formed the nucleus of a group of remarkable productivity and stability.^(b)

The first contract was between the University of Washington and the U.S. Office of Scientific Research and Development. No possible connection between the radiation studies they were about to undertake and the construction work at Hanford could be permitted.^(c) Thus, no association with the MED could be countenanced. The contract was let on August 15, 1943. Work with x rays on embryos, larvae, and fingerlings as well as adult salmon, and later trout, began as soon as equipment could be installed.^(d)

The work on immature stages of fish indicated what we now know well—greater sensitivity to radiation than for adults of the same species. However, the sensitivities were not so different from those of terrestrial forms of life as to

(a) These and many other details can be gleaned from chapter 1 of the beautifully written and authoritative documentary book by Neal Hines entitled *Proving Ground* (Hines 1962) and the equally attractive chapter by Foster in a later book that brings together in depth the tremendous efforts expended on the potential problems of the Columbia River and its estuary (Foster 1972).

(b) They are still producing despite theoretical retirements.

(c) It was fortunate indeed that Foster and Welander had already been interested in the effects of radiation on fish. Not only were they prepared, but the new work could be easily viewed as an extension of their former interests.

(d) Hines tells that Francis Bishop, a key radiological technician from the University of Rochester, came to Seattle to help install the x-ray equipment in a hurry.

predict cataclysmic effects on the fish population. There did seem to be somewhat more delay in the expression of the effects in the aquatic forms, possibly because of the lower body temperatures in general. While much of the work with adults utilized fairly high doses, the really interesting work involved low and moderate doses. Such doses were given to young adult fish that would go to sea for two years or more. It was the effect on the numbers and health of the fish returning to spawn that was the key question. Such work was possible because of the remarkable homing instinct of salmon to spawn in the same place, *exactly*, that they left to go to sea.

However, the answers to these questions were at least two years away. The effects of Hanford pile effluents needed immediate attention. Thus, the venue for this exposition shifts from Seattle to the Hanford site^(a) and from x rays to pile effluents. In early 1945, Foster was moved to Hanford and set up in a Quonset hutment near one of the reactors. This was called the Fisheries Laboratory and was built as sort of a swan song by some of the construction workers finishing off the adjacent reactor complex. It is pictured in figure 11.1.

Two types of work proceeded at this facility: (1) exposure of fingerlings to various concentrations of pile effluents in troughs reminiscent of fish hatcheries the country over to measure possible deleterious effects, and (2) the uptake and retention by the fish of radionuclides from the pile effluent stream. In addition, studies were begun in 1946 on the river itself—its fish, the plankton, the dilution

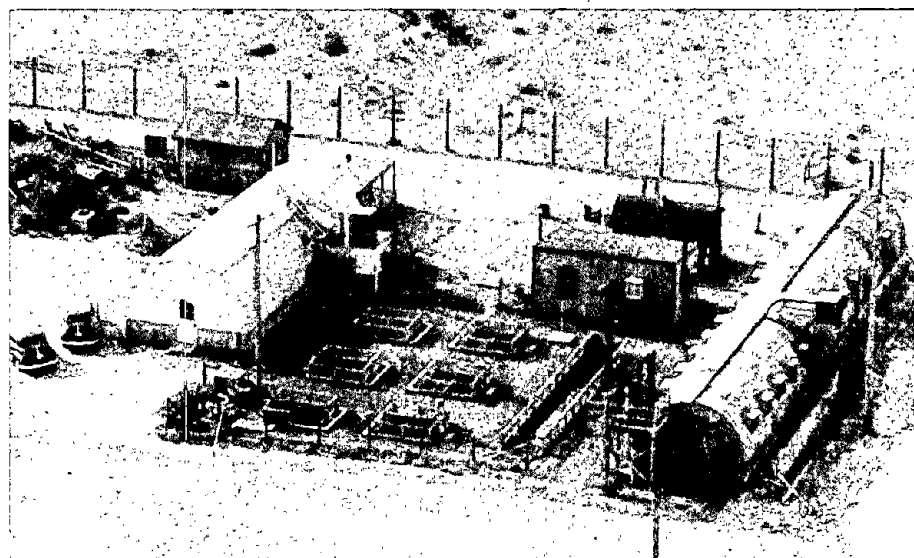


FIGURE 11.1. The Fisheries Laboratory (Building 146-F) at the Hanford plant during the MED days. (Photograph courtesy of Pacific Northwest Laboratory.)

(a) The continuing x-ray work at the Applied Fisheries Laboratory is nicely summarized by Hines and by Foster. Indeed, Hines gives a complete listing of the University of Washington Fisheries Laboratory reports (UWFL series). This work is somewhat outside of our purview because it did not use radioactive materials, and we must forego the impulse to describe it in detail. It was absolutely basic to the whole enterprise and expertly done.

and distribution downstream of the effluents, effects of the warm water from the reactor on the temperature of the river, and gradually the entire aquatic ecosystem.

The story of this research is available in depth in the chapters by Hines and by Foster and in the literature cited therein. "By 1949 the laboratory and river studies at Hanford had shown that the fisheries resources of the Columbia River were not threatened by the plutonium plant and that there was no radiation hazard to people who used the river and its fish" (Foster 1972, p. 8). Indeed, process chemicals in the reactor effluent, such as sodium dichromate, showed greater potential toxicity to aquatic life than the amounts of radionuclides discharged. Only a factor of ten separated the usual concentrations of these in the river near the piles and known toxic levels.

There were some surprises, however (Foster 1979). At the beginning, only gross radioactivities were measured. Separation of isotopes was not yet routine. As techniques developed for identifying radioactive materials, it became apparent that those present in the river were largely products of neutron activation of substances already present in the river water and components of the pile structures. However, there were more fission products present than any reasonable prediction of fuel element leakage would support. Also, the concentrations were more or less constant, not released in puffs as would be expected from occasional leaks in the fuel elements. This turned out to be due to activation of "tramp uranium" already present in the river water.

Another surprise was that the activity in fish from the river was substantially greater than that in fish from the laboratory exposed to pile effluents. This puzzler was explained by the fact that the laboratory fish were being fed uncontaminated food, whereas the river fish got their food from natural sources that contained normal radioactivity (not increased much by the reactors). This led to the elucidation of the importance of the food chain and of concentration in organisms of some of the elements by specific metabolic processes.

Yet another surprise was the finding of a qualitative difference in the elements in laboratory versus river fish. The radioactivity of laboratory fish came from elements like sodium and other short-lived materials that were easily assimilated from the surrounding water. By contrast, the fish from the river showed high concentrations of substances like ^{32}P , which had been concentrated from nutrients. Thus, again the importance of metabolic processes in concentrating radionuclides from the environment and of the food chain was highlighted.

Another finding that was not fully expected was the presence of sufficient amounts of ^{51}Cr to have it present, indeed predominant, at the mouth of the Columbia. As remarked earlier, sodium dichromate was added to the intake water of the reactors as an algicide. Activation of the stable chromium in the neutron flux of the reactors generated the ^{51}Cr . Even so, it was the nonactivated stable chromium in the released sodium dichromate that posed the principal immediate toxic hazard to aquatic life of the Columbia River.

In essence, the war work gave clear answers to the original question—toxicity of the pile effluents^(a) in the short term. However, the need for measurement

(a) We should add that back at Seattle the salmon that had received low radiation doses before going to sea were now returning in numbers and were in no worse shape than nonirradiated cohorts after two years of buffeting in the fierce marine environment.

of more subtle long-term effects was apparent. Also, the behavior of radionuclides in aquatic environments was only beginning to show its potential ramifications. It is not surprising, therefore, that more permanent facilities and long-term staff commitments developed at both Hanford and Seattle after the war, as we shall see in the next section.

The Hanford ecology effort during World War II was not confined to aquatic biology. As related in earlier chapters, it was known that radionuclides such as radioiodine and radioruthenium were being released in small but measurable quantities from the facilities. Radioiodine was easily found in the thyroid of jack rabbits on the site. However, there was concern over the cattle in the environs of the plant, especially some that were on the opposite side of the Columbia. How could some measurements be made without breaking the tight security as to what was going on at the plant? A graphic description of how one set of measurements was made is contained in the following excerpt from a communication sent to this author by Karl Herde:^(a)

In the summer of 1946 several herds of cattle frequently were seen grazing on AEC property [sic] across the river from Hanford reactors and separations plants on land generally known as the Wahluke Slope. Iodine-131 releases were not at that early date well controlled and were known to have resulted in significant concentrations in rabbits, goats and sheep on the plant site. Concentrations in the thyroids of Wahluke Slope cattle were unknown and a challenge to those responsible for monitoring.

The Manhattan Engineering District Manager was asked to cooperate in making a survey possible. A request for volunteers was sent down the line through the U.S. Army Component then stationed at Camp Hanford. Six volunteers selected because of "special western ranch experiences" reported to the writer in a jeep and two 4-wheel drive weapons carriers at the Hanford Ferry early one July morning. Each vehicle had a 50-foot length of new manila rope that was to be used for lariats and at least two of the G.I. volunteers wore cowboy boots and ten-gallon hats to prove their "suitability" for this special job.

After crossing the Hanford Ferry the fleet of three vehicles journeyed along the river past several abandoned farm sites before taking trails that led to the slope where a herd had been spotted. Two vehicles carried "Pfc cow-pokes" with coiled lassoes. The other carried biologists with a primitive portable geiger counter. At the first approach the herd showed little alarm, the two "ropers" agreed to cast their ropes simultaneously at two big steers near the outside. The ropes fell short by about one third the distance and the cattle stampeded. Each vehicle pursued a dogie and a long dusty chase began. Time after time lariats missed target. It was obvious that no special talent was riding the range. After the humiliation of many failures, and the slowing down of the dogies the ropers tried bull-dogging. As the animal was ready to fall from exhaustion the "bulldoggers" plunged victoriously upon it, slipped a rope over its head with a half-hitch on a foot, and stood triumphantly over the wheezing prize.

External thyroid counts being surprisingly low and observing no physical injury to animals, the team was asked to capture and monitor another pair from this herd.

A second herd located further west in the vicinity of White Bluff was similarly "scientifically sampled." Fortunately in neither case did we encounter owners of the herds. Since this was off-limits, the farmers were content to let the cattle drift out unattended. We suspected that the ranchers deliberately scheduled their round-ups of the herds during the dark hours. Though somewhat higher in thyroid

(a) Karl Herde was among the early workers in the Hanford group and the first professional biologist assigned to the Biology Group. He later went to Savannah River from which he is now retired. I am indebted to him for these anecdotal descriptions.

readings, the levels monitored were calculated to be of no health hazard to the cattle nor to persons handling the animals or consuming the meat. Several vegetation samples were collected from each location in order to facilitate a comparison between the food consumed and thyroid activity.

In a conference to evaluate and analyze the thyroid data no special concern was felt for the animals of Wahluke Slope nor their owners who lived beyond the crest of Saddle Mountains or on the plateau to the east. However, it focused attention on other areas. The prevailing winds were favorable to the Slope, but what about the more populated and intensely farmed valley of the Yakima River? Smaller farm herds from the irrigated area from Toppenish to Benton City should be monitored and this could not be accomplished as completely secretive as we had monitored animals of the Wahluke Slope. This need was passed on to the Security Division of the Manhattan Engineering District and became another historic venture in biological monitoring, that is the subject of another episode report.

The Wahluke Slope monitoring produced no striking results but was a positive factor in selling the needs for an experimental animal farm that became a reality at the 100-F Area in 1948. (Herde 1978)

It took a more subtle approach to get data on thyroid activity from cattle in the Yakima River valley mentioned by Herde in the quotation above. Excerpts from his description of that operation are given below:

Though the Environmental Survey Group at Hanford had been sampling air, soil, water, and vegetation in a wide area surrounding the Hanford site for several years previous to 1946, it was agreed that sampling farm animals for uptake of fission product plant wastes would be a much more sensitive problem. At that time the revelation of a regional iodine-131 problem would have had a tremendous public relations impact and furthermore the presence of other nuclides (some known but some not recognized or identified) was of possible National Defense significance.

I was called at my home before work hours and asked to report, not to my area office, but to the Director's office in downtown Richland, for instructions upon a full day's trip off the site. I was advised to dress in field clothing, preferably khaki shirt and pants, a tie and leather jacket. Once in the Headquarter's Office I was introduced to two Security Agents of the Manhattan Engineering District (MED) who were to be my escorts and contact men during the day. They proved to be the best straight-faced "liars" I had ever known. I was no longer "Karl Herde of Du Pont" but through that day would be known and introduced as Dr. George Herd, of the U.S. Department of Agriculture. I was to simulate an Animal Husbandry specialist who had the responsibility of testing a new portable instrument based on an unproven theory that by external readings on the surface of farm animals the "health and vigor" of animals could be evaluated. I was advised not to be alarmed if at times during conversations with farmers that they appeared critical or skeptical. I was to be very reserved and answer questions as briefly and as vaguely as seemed acceptable. They agreed to carry a clip board to write down essential data on the location, size of herds, approximate age of animals, and general comments. I was to concentrate upon the high readings (thyroids, of course) and furnish those for recording when not being observed.

That day we visited several diversified farms under irrigation from the Yakima River between Toppenish and Benton City. Livestock observed and monitored included horses, cattle, and sheep. Smooth talk and flattery enabled us to gain one hundred percent cooperation. Farmers were most interested in measuring the sire of the herd. Ironically to me, the thyroid activities of these were usually lower than average due to increased confinement upon a regimen of dry feeding.

Animals were either run into stocks or stanchions or were haltered and tied during the survey. Numerous measurements were made, usually in the flanks, scrotum, udder, and neck with "emphasis on the jugular vein." While "measuring the jugular" I was successful in placing the probe of the instrument directly over

the thyroid at times when the owner's attention was focused on the next animal or some concocted distraction.

This clandestine monitoring was possible at that time only because of the general secrecy that still prevailed around the atomic energy program. (Note the use of lower case, as there was no Atomic Energy Commission at that time.) The geiger-counter was known to professional physicists but did not become a household word until several years later when prospecting for uranium and measuring fallout from weapons testing made it famous.

Instruments used at Hanford were intentionally named to be misleading lest they be associated with the product or the mission of the site. The instrument used was called a "G.M. Counter," but on that particular day it was called the "thing," "your gadget," or your "brain-child" as if my colleagues were skeptical. It may be of interest to recall that during the war an instrument specialist had developed a new "sniffing instrument" for which he proposed the name Pluto, in honor of Pluto the Pup, a cartoon character. General Leslie Groves of MED censored the name since it might suggest plutonium as a product of this highly secretive plant.

Positive, though low thyroid readings in nearly every animal examined helped establish the basis for an experimental animal farm which was planned and sold by the writer and colleagues and built in 1948 at 100-F Area.

At the Experimental Animal Farm the health significance of various intakes of iodine-131 and its subsequent accumulation in thyroids was evaluated for sheep, cattle, and swine [chapter 8]. Based upon that research and such biological monitoring as reported above we were able to say that it is very unlikely that animals or persons consuming milk and meat products grown in the vicinity of Hanford were in any case damaged. (Herde 1978)

Before we leave the years of World War II, we should be reminded that the Metallurgical Laboratory at Chicago did some work on the uptake of fission products by goldfish (see chapter 7, work by C. L. Prosser et al.). The distribution was quite like that seen in terrestrial mammals.^(a)

III. The Early Postwar Years

A. Continuation of Hanford Work

Unlike the major changes wrought at many of the MED laboratories by the transition from wartime to peacetime endeavors, most programs at Hanford continued almost without a pause. Even the transition from the Du Pont Company to the General Electric Company as prime contractor made little immediate difference in programs. This was especially true of the environmental biology work. True, the investigators now knew why they were doing the work, and the gradual lifting of security restrictions allowed much more communication among segments of the enterprise, particularly between Hanford and the University of Washington. The primary change was an increase in effort and momentum.

The very first annual report of biology research^(b), covering the year 1951 and published in April 1952 (Hanford Works 1952), contained the following summary

- (a) At the time of review of this work in chapter 7, we wondered if the Met Lab people did this out of idle curiosity or for other reasons. Since we have now seen the depth of interest of Stafford Warren and others in fisheries problems, we might conclude that the goldfish work was more than idle curiosity.
- (b) The biology section of the report contained programs on aquatic biology, metabolism of radionuclides, toxicology, and biological services as part of the Radiological Sciences Department.

by R. F. Foster of work on the biological problems associated with the discharge of pile effluent into the Columbia River:

The location of the Hanford Works on the banks of the Columbia River has raised many questions of possible effect on the aquatic life. Such questions were initially prompted by concern for the economically valuable salmon and other fisheries resources supported by the Columbia and by concern for the hazard which might result from utilizing local game fish as food. To answer some of these, an aquatic biology laboratory was established soon after operations were started, and from this beginning an integrated program of research on organisms of the Columbia River developed.

Large volumes of Columbia River water passed through the nuclear reactors as coolant are ultimately returned to the river. This pile cooling water, or effluent, constitutes a potential hazard to aquatic life since it is hot, mildly radioactive, and contains certain toxic chemicals. Investigation of the actual or potential effect of this effluent on the biota of the Columbia River is the principal objective of the Aquatic Biology Unit, and basic approaches involve both laboratory experiments and field observations.

One group of laboratory studies is designed to determine the dilution level at which adverse effects are first apparent, and further whether such effects are due to radioactivity, chemical toxicity, temperature, or some combination of these factors. Since operating conditions for the reactors are subject to change and since irregularities could occur at any time which might increase the hazard to aquatic forms, subjection of organisms to dilution of the pile effluent is continued throughout the year and from one year to the next as a type of biological monitoring. Young salmon and trout are used as test animals for these studies since they represent species of economic value and also appear to be among the forms most sensitive to the effluent water. The chinook salmon are of particular interest since a substantial portion of the fall run of this species spawns in this section of the river.

It is not possible under laboratory conditions to duplicate or even closely approach all of the environmental factors present in the river, and many complex and delicate ecological relationships and balances are in operation which conceivably could be affected by the effluent. Field studies were therefore undertaken in order to determine the natural ecology of the river and the biological conditions of that section of the river which receives effluent from the pile areas. These studies include: (a) comparing such characteristics of the aquatic communities as species abundance above and below the effluent outlets, (b) determining seasonal variations in these communities and (c) determining various interspecific relationships such as food chains. Associated with the ecological studies, radioactivity measurements are taken of the various river organisms. From these measurements it is possible to determine which isotopes present in the pile effluent are concentrated in the river organisms in significant amounts, which organisms become most radioactive, the distribution pattern of the radioactivity in the river, the seasonal fluctuations and their significance, whether the organisms are receiving radiation that may affect them or their progeny, and the extent of the hazard to humans utilizing river fish for food.

Certain isotopes present in the effluent water, notably P^{32} , are substantially concentrated in the aquatic forms of the river. This concentration is responsible for the greatest part of the potential radiation hazard, and adequate knowledge of the mechanism of this concentration is desirable in order to permit a rational approach to its control. While the plants concentrate radioactive isotopes directly from the surrounding water, the higher animals obtain these isotopes not so much from the water as from the lower forms upon which they feed. Thus the food chain is of prime importance in determining the ultimate levels of activity density attained by the higher organisms, including the fish. The susceptibility of the lower forms of life to the pile effluent takes on added significance in view of their role of sustaining

the economically valuable species. The determination of the rates at which representative forms pick up radioactivity from the environment, the importance of various types of food organisms in accumulating and transferring the radioactive materials, the levels to which specific isotopes become concentrated in the organisms, and the rates of elimination of radioactivity or biological turnover, constitute another area of research to which some attention has been given and from which we may hope to gain suitable explanations for observed levels of radioactivity in the river biota. (Foster 1952)

This summary is followed by details on spawning and migration of Chinook salmon in the river in the vicinity of Hanford, radioactivity of aquatic organisms, transfer of pile effluent to trout, effects of pile effluent on fish, etc.^(a) A graph from this early report showing the geographical distribution of radioactivity in snails from various sections of the river is shown as figure 11.2.

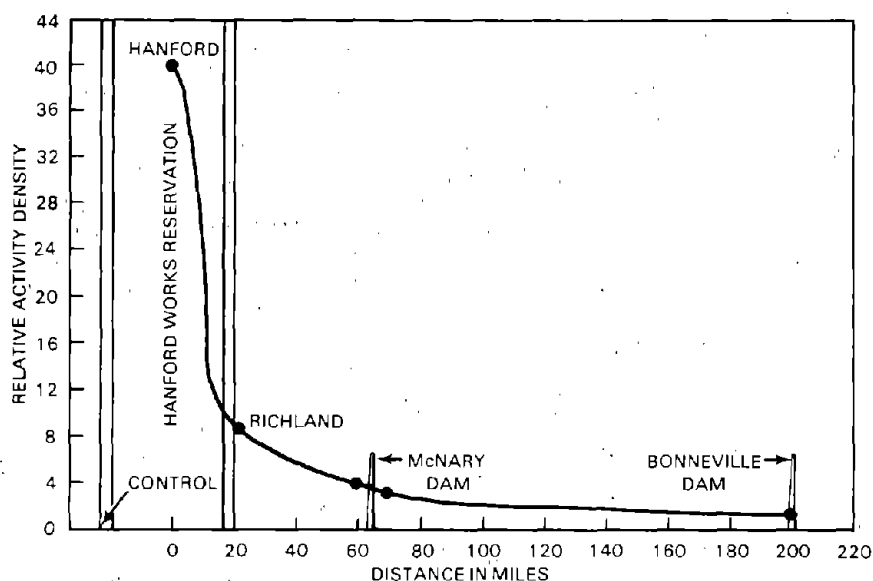


FIGURE 11.2. Geographical distribution of "radiation density" in snails sampled during September 1952. (Redrawn from Davis et al. 1952.)

In this first annual report, we are also made aware that a sizable program of terrestrial ecology was under way.^(b) It was hidden away under the broad title, "Biological Monitoring" (Hanson and Browning 1952) and concerned the ^{131}I in the thyroid tissues of jack rabbits collected near the separations plants and radioactivity in ducks maintained at a disposal ditch containing fission products. The most interesting finding was that the concentration of fission products in

(a) The earliest reports were in the classified HW series and bear the names of Herde, Coopey, Davis, Palmer, Watson, Honstead, and others. Some of these are cited by Foster in his introduction to the Pruter-Alverson volume (1972). See, for example, Davis et al. 1952. Others, such as J. Corley and J. Soldat appeared as the work progressed.

(b) In chapters 8 and 9, we learned that iodine from the plant sites was one of the first airborne contaminants identified, and that ruthenium particles led to the first concern about the inhalation of "hot particles."

bone of the ducks was from 102 to 105 times that of the water, no surprise now, but it impressed the early investigators. The report cites originally secret documents by Herde, Cline, Hanson, and Browning.

At the first International Conference on the Peaceful Uses of Atomic Energy (held in Geneva, Switzerland, in 1955 [proceedings published in 1956]) Foster and Davis summarized work on the accumulation of radioactive substances in aquatic forms; Hanson and Kornberg discussed radioactivity in terrestrial animals near the site; Rediske and Hungate described the absorption of fission products by plants; and Parker gave a general review of radiation exposure from environmental sources.

The first-named review (Foster and Davis 1956) showed that radioactivity (called "radioactivity density") could vary by an order of magnitude in plankton versus fish; that the aquatic plants picked up substantial quantities by adsorption on their extensive surfaces; that scales of fish contained the highest concentrations followed by bone, liver, kidney, etc., just as in terrestrial organisms; and that the concentrations in plankton and other organisms decreased rapidly with distance from Hanford, as was shown for snails in figure 11.2.

The second-named review (Hanson and Kornberg 1956) showed ratios of ^{32}P in adults, eggs, and young of birds and the sometimes high but quite variable ratio of amount in bird to amount in water and that the amounts deposited had no effect on hatchability of eggs or fertility of adults. They also gave a breakdown of the isotope composition of swamp water, vegetation, bird muscle, and bird bone (they differed markedly). They reported that relative ^{131}I concentrations could range from 100 in rabbit thyroid to 20 in coyotes to 1 in insects and 0.2 in vegetation, the latter two considered as staple food items for the animals studied.

The Parker paper (Parker 1956) presented a capsule classification of the hazards that could be expected around various types of reactors, around chemical processing plants, and potential exposure mechanisms. While brief, even cryptic, this exposition is remarkably prescient and complete. It gives a glimpse of the fact that even in the early postwar years the groundwork had been laid for most of what followed. This included air, water, vegetation, animal, and aquatic biota sampling, as well as the encouragement of research under controlled laboratory and environmental conditions. H. M. Parker was behind all of it.

During these years (decade of the 1950s), the Hanford crew did much of the work, even rather distant from the site without a great deal of collaborative help except from the University of Washington Applied Fisheries Laboratory. Representatives of various state and government agencies were invited in to see what had been going on during the war and what was under way at the time. This occurred in 1945 and 1946, soon after the lid of secrecy had been partially sprung (Foster 1972). There was a Columbia River Advisory Group established by the Atomic Energy Commission (AEC) in 1949 to "provide advice and program direction and waste disposal procedures." This included appropriate state agencies of Oregon and Washington and the regional office of the U.S. Public Health Service (PHS). It met periodically over a period of fifteen years or so.

In 1950, the Public Health Service sent an ecology team to Hanford. They worked for about two years and amply confirmed the major findings of the Hanford people (see Robeck, Henderson, and Palange 1954). Nevertheless, the bulk of the work was conceived and implemented from Hanford and the University of Washington.

On the occasion of a personal visit to Hanford during the 1950s, it was this author's privilege to see both the laboratory and field work, albeit somewhat superficially. He met the crew and saw the thirty-foot biology boat fitted out with many special home-built devices for controlled water sampling and other activities. This palatial craft is pictured in figure 11.3, courtesy of J. Soldat and his capacious files.

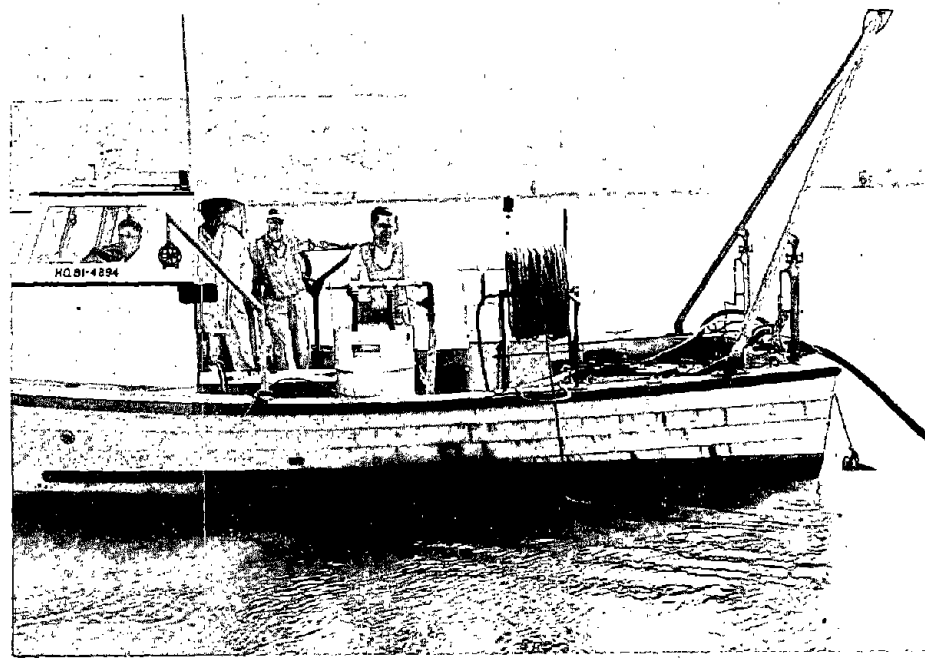


FIGURE 11.3. Biology boat used for sampling in Columbia River in early days (courtesy of J. Soldat, Pacific Northwest Laboratory [PNL]).

The work of this and similar craft and crews led to the clear identification of radioactive materials from the Hanford site not only in the Columbia River estuary, but in the Pacific Ocean far beyond the mouth of the river. Description of these findings will await our discussion of the later postwar years.

A different aspect of the Hanford early postwar work was displayed at the second Atoms for Peace Conference. This was held in Geneva, Switzerland, in 1958. Healy and coworkers presented what was probably the first publication intended for a broad audience on the potential radiation exposure of people in the environs of a major atomic energy plant,^(a) viz., Hanford (Healy et al. 1959). The estimates of dosage were made for the year 1957, a year when fallout from nuclear weapons tests was significant, but the authors were able to "correct" for this. The chief caveat in this early report concerning a production site was that

(a) There were others, but these were theoretical analyses of possible reactor accidents (e.g., Kuper and Cowan 1959). These are not our subject here.

the operations were not representative of the nuclear power plants of later years. The reactors used once-through water cooling, and there were large chemical separations plants on the site also.

They developed what we would now call a source term from data on releases; they measured air concentrations, vegetation contamination, etc.; they measured concentrations in river and drinking water and in food such as whitefish flesh^(a) and edible duck flesh; they identified isotopes from irrigated land and in the river water; they followed variations with time of the year; and they presented the results as percentage of maximum permissible limits. The data included bone, thyroid, gastrointestinal tract, and gonads. The only values that were above (slightly) the then-permitted population limit occurred in the gastrointestinal tract at the perimeter of the plant site in June and October and at a distance greater than 60 km, also in October. However, many of the other values for gastrointestinal-tract exposure were appreciable fractions of the population limit. The final values calculated for total exposure to internal emitters from several sources is shown in table 11.1:

TABLE 11.1. Total Exposures at Plant Perimeter (Hanford) from Internal Emitters—Percentage of Maximum Permissible Limits.

	Bone	Thyroid	GI	Lungs
Drinking Water	3	2	20	—
Air	—	0.03	—	0.1
Vegetation	2*	3	40*	—
Fish	20†	—	6†	—
Waterfowl	25†	—	8†	—

*Excluding Sr⁹⁰; remainder primarily from nuclear detonations.

†Maximum to very small portion of population.

Note: Strontium-90 was omitted because of variability in its contribution. Bone samples indicated accumulation of less than 1% of the maximum permissible.

Source: Reset from Healy et al. 1959, p. 455. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1959.

At this same Geneva Conference, we get a glimpse of another Hanford interest: dispersion of contamination by wind (Healy and Fuquay 1959). This is of special concern in arid regions such as Hanford and the Nevada Test Site (NTS) and will be discussed in connection with the "safety tests" (chapter 14) and environmental transport (chapter 15).

Leo Bustad, whose work with iodine we met in chapter 8, gave a succinct review of Hanford work in relation to animal populations in the environment at a symposium on radioisotopes in the biosphere (Bustad 1960). He showed the concentrations of eleven isotopes in fish, ⁶⁵Zn concentration in a beef cow, accumulation of radioisotopes from drinking water by rats, and the concentrations and behavior of iodine. He tied this information to the ongoing

(a) Richard (Dick) Foster, whom we have already met as director of the Hanford aquatic biology operation, is reported to have routinely eaten, each Friday night, at least eight ounces of whitefish caught in the Columbia near Hanford. Later, when whole-body counting became common, he was a regular and willing subject. So far as this author knows, his count always remained within normal limits.

animal-farm experiments, considered the Hanford plant's limits for population exposure, and concluded that the population exposures were "inconsequential."

A cogent chapter in the same symposium by Hanson, which drew also upon Hanford experiences, concerned iodine in the environment (Hanson 1963). This covered nearly every aspect of iodine in the environment and showed how far along the field was even in the early 1960s. It included information on the effects of iodine as well as its transport.

At the same meeting, Harry Kornberg, manager of the Hanford biology operation, presented work on the passage of pairs of elements through food chains. We will have much occasion to review the data and concepts developed on this subject when we review fallout and experimental work arising out of the fallout problems (chapter 13).

A later review by Foster on environmental behavior of chromium and neptunium revealed yet another facet of the work at Hanford (Foster 1963). Also, J. J. Davis discussed the relationships between cesium and potassium (Davis 1963). These, like the other papers in the session, were broad reviews of the subject, but drew their illustrations from the information gathered in Hanford work.

A comprehensive summary on the Columbia River estuary is given in the book by Pruter and Alverson (1972). This work was the result of studies suggested by Gene Wallen in the Ecology Branch of the AEC Headquarters Division of Biology and Medicine directed by John Wolfe. Also, the Oregon Board of Health coordinated a series of whole-body counts on residents of a community on the Oregon Coast near the mouth of the Columbia River. These individuals were largely fishermen, seafood processors, and avid consumers of seafood. Their whole-body counts remained within the range of those associated with fallout radionuclides.

Obviously, by the end of the first decade plus a few years after the end of World War II, radioecology was beginning to prosper, and one of its prime centers was the Hanford Atomic Products Operation.

B. Enter Oak Ridge^(a)

Except for routine industrial-hygiene-type practices, expanded to include measurements of air and waterborne radioactivity, the Clinton Laboratories had no research program during the war years directed primarily at environmental concerns. Their waste disposal practices of the MED days involved largely impoundments and basins that were not lined with concrete or otherwise isolated from the environment except for high fences. In the early postwar years, Karl Z. Morgan, director of the Health Physics Division of Oak Ridge National Laboratory (ORNL), became increasingly concerned about the potential for release of contamination to the environment from these and its possible impact. The largest single impoundment was White Oak Lake, which was developed by placing a dam across White Oak Creek. It had received radioactive waste throughout the war years.

(a) Much of the information used in this description of the earlier days of the Oak Ridge ecology program comes from a taped interview with Stanley Auerbach, chief of the Environmental Sciences Division, Oak Ridge National Laboratory (Auerbach 1979) and the introduction and historical perspective to the excellent, two-volume book by Ward Whicker and Vincent Schultz (Whicker and Schultz 1982).

The first step was collaborative work with ecologically trained biologists from the Tennessee Valley Authority (TVA). One of these was a fisheries biologist, L. A. Krumholz, who has remained identified with radioecology ever since. Others taking part were a botanist, Nease, and two limnologists, Ross and Helm. The program was established in 1950, developed some momentum, and completed several ORO^(a) reports on several aspects of the flora and fauna and on the concentrations and behavior of contaminating radionuclides in White Oak Lake and its environs.

The group found ample amounts of radioactivity, identified many of the isotopes, and made a start on measuring their behavior in the environment. They could find no evidence of deleterious effects on aquatic or terrestrial populations. This led many segments of management to conclude all was well and that the work could be phased out. After all, this was a fairly highly contaminated area. A further factor was the presence of wide variations in results of work attempting to measure the impact of low-level radiation on the site, even the behavior of the radionuclides themselves. The presence of multiple factors characteristic of environmental work and the remarkable ability of complex ecosystems to accommodate to perturbations made for much of this variability. It did not surprise the ecologists, but it struck horror in the minds of physicists, chemists, and mathematicians who constituted a very influential force at Oak Ridge National Laboratory.

Several events occurred, however, that saved the Oak Ridge environmental program from obliteration. First, Karl Morgan mounted a crusade for continuation of the work. In his mind the real science lay ahead. He emphasized that what had been done so far was only preliminary and range-finding in nature. Second, it was decided to drain White Oak Lake! This was due to concern that a several-inch downpour of rain, not unknown in that part of the country, might cause the impoundment to overflow, even carry away the dam. Hence, the former lake bed was to become a meadow with a meandering stream and a dam that could be closed for flood-control purposes. Here was a natural contaminated ecosystem fully ripe for detailed investigation.

A third factor was the presence in high echelons of Eugene Wigner and others who had keen interests in the future of nuclear power and knew that radioactive waste disposal would be a key problem in any such development. Morgan persuaded management to transfer Edward Struxness, who was supervisor of health physics at the Y-12 plant, to the Health Physics Division of the laboratory to begin some scientific work on waste-management problems. Struxness, like Morgan, had considerable empathy for the environment. He had taken ecology courses during the war years and after. To him, "improving the waste management programs" meant research on and in the environment.

Soon Dr. Orlando Park, professor of ecology at Northwestern University who had taught Struxness, was brought in as a consultant and helped to map out the program. In 1954, Stanley Auerbach, who had done his Ph.D. work with Park, was persuaded to join the fledgling group. In 1965, a budget for 1.7 man-years (\$56,000) was earmarked for the program.

It was not out of the woods, however. Ecology was a strange subject to many of the good people at AEC Headquarters. They could see the need for large biology programs of more conventional nature as described in earlier chapters of this book, even the "megamouse" genetics program, but not the utility of a

(a) ORO = Oak Ridge Operations Office.

broadly based ecology enterprise. The idea was still widely held that if man was acceptably protected, his environment would automatically be protected. The fact that man is "an integral part of his environment" (Whicker and Schultz 1982, p. 5) had not yet become generally appreciated.^(a)

Both Auerbach and Whicker and Schultz indicate that much of the further development of radioecology at Oak Ridge and in the United States, generally beyond the programs already under way, was "due to the farsighted vision and encouragement of Charles Dunham (M.D.) who became chief of the Division of Biology and Medicine (DBM) of AEC in 1955" (Whicker and Schultz 1982, p. 6). By 1958, an Environmental Sciences Branch was developed within the DBM, and the capable Dr. John Wolfe, an ecologist from Ohio State University who had helped the DBM as a consultant, was persuaded to assume its direction. From this point on, funding for environmental aspects ceased to be a constant battle. In fiscal year 1970, the budget was \$18.9 million, divided into \$6 million for terrestrial and fresh water ecology, \$4 million for marine sciences, and \$8.9 million for atmospheric radioactivity and fallout (Whicker and Schultz 1982, p. 6). Only the first category helped to support the Oak Ridge program, of course.^(b)

A further stimulus was the finding of an osteogenic sarcoma in a muskrat with a heavy body burden of ^{90}Sr caught in the White Oak Lake area.

The first serious work in the revitalized Oak Ridge program was much more than an extension of the earlier TVA-ORNL collaborative effort. The White Oak Lake site gave an opportunity to address key questions of considerable ecological importance but of great technical difficulty. White Oak Lake had been drained, and the environmental group began probing the behavior of the principal isotopes in the old lake bed, e.g., ^{90}Sr , ^{137}Cs , ^{60}Co , and ^{106}Ru . Also, the several waste pits were known to be leaking, and the environmental sciences section decided to see to what extent trees might act as accumulators of the various isotopes. Because of lack of information on the underground hydrology, the results were again difficult to interpret. Some trees were "hot," others were not. There followed much work on the transfer systems, especially food chains in the lake bed and other areas. Also, they began inoculating trees with known doses of isotopes. Transfer coefficients and food chain components were identified from this work. A picture of the inoculating procedure is shown in figure 11.4.

In the 1960s, Auerbach and his growing group considered that a real ecosystem experiment could be started. They chose ^{137}Cs because it was in both fallout and nuclear plant waste and had mobility, convenient half-life, etc. They chose the tulip poplar because it is a common and important tree in the southeast. They inoculated a stand of these with 500 mCi of ^{137}Cs proportioned among the trees according to size. The results, published over many succeeding years and thus partly belonging to the era discussed in section V of this chapter, showed

- (a) It is somewhat paradoxical that all of these difficulties were occurring while the Hanford and University of Washington programs were sailing along splendidly. Perhaps one reason was that the Columbia River Project was, much of it, financed from operating rather than research funds. Obviously, the tie-in to major fisheries problems did no harm.
- (b) We will examine the others in later sections of this chapter and in chapter 12. When we contemplate the excellence of the staff and work of the present Environmental Sciences Division of ORNL and its facilities (see section V), we can feel only relief and satisfaction that the original organizers persevered.

FIGURE 11.4. Inoculating trees with radioisotopes—Oak Ridge Ecological Research (Auerbach and Schultz 1962).



that most of the cesium was cycling out of the trees into the litter on the forest floor. The litter protected the root zone from rapid re-entry into the system because there were several inches to traverse. Recycling in the trees was therefore slow. However, processes occurring in the litter and exposure of other organisms to the radioactivity in the litter could be important.

Work with mammals was accelerated by adding Paul Dunaway and later Stephen Kaye, to help him. Kaye later headed up the environmental sciences work.^(a) Among other things, changes in the blood picture of the native rodents were investigated.

Obviously, the Clinch River was the object of many investigations beginning even in the early 1950s. This system was hardly the all-consuming effort that the Columbia River system was, but it had many features in common. In 1962, the DBM of AEC produced a summary report concerning the onsite ecological research at ORNL (Auerbach and Schultz 1962). The headings for projects in the aquatic studies section are reproduced below to give the flavor of the enterprise:

Aquatic Studies. . . .

The suspended microbiota of the Clinch River and adjacent waters, in relation to radioactivity in the summer of 1956.

Uptake of cesium-137 by cells and detritus of *Euglena* and *Chlorella*.

(a) Kaye directed the Health and Safety program in the early 1980s.

The role of the fresh-water crayfish as an agent in strontium concentration.

Analysis of the bottom organisms from Clinch River mile 23 to Tennessee River mile 560.

The role of heterotrophic microorganisms in the concentration of specific radionuclides on organic matter.

Uptake and elimination of cobalt-60 by a species of crayfish, *Cambarus longulus longirostris*.

The role of tubificid worms in the transport of radioactive bottom sediments in the Clinch River.

The biogeochemistry of strontium and calcium in mollusks of the Clinch and Tennessee Rivers.

The effect of effluent atomic wastes on *Chironomus tentans* Fabricius population as determined by salivary gland chromosome analysis.

The biogeochemistry of strontium and cesium in the white crappie (*Pomoxis annularis*).

Application of radionuclide uptake and bioaccumulation data to the study of fish population dynamics.

(Auerbach and Schultz 1962)

A similar summary listing for research in terrestrial areas contaminated by radioactive wastes includes work with trees; crops; insect-bird food chains; accumulation of isotopes in grasshoppers; radiation effects on two species of sedge; surveys of mammals and other vertebrates, including pathological conditions found; and much on the movement of key radionuclides. Much of this work contributed to the designation of "critical pathways" in calculating population exposures (see chapter 15).

Specifics from the Oak Ridge ecology program of these earlier years can be gleaned from reviews prepared for the same volumes already cited for the Hanford work. At the first radioecology symposium, we find papers on radiostrontium and radiocesium in insects (Crossley 1963); bioaccumulation of radionuclides in mammals (Kaye and Dunaway 1963); an analogue computer model for the movement of nuclides through ecosystems (Olson^(a) 1963); cycling of ¹³⁴Cs in White Oak trees (Witherspoon 1963); strontium and calcium relationships in the Clinch and Tennessee Rivers (Nelson 1963); effects on the mammal populations of the White Oak Lake bed (Dunaway and Kaye 1963); changes in salivary gland chromosomes of larvae of an insect population (Nelson and Blaylock 1963); biological and environmental behavior of ruthenium and rhodium (Auerbach and Olson 1963); and various ways in which radioactive tracers were used to study movement of animals, decomposition of forest litter, food chains, etc.

The body burdens of several radionuclides in muskrats from the White Oak Lake bed are given in table 11.2, which shows that the amounts are not insignificant and that large variations are characteristically seen. One of the important needs for future work developed from these programs is to explain these variations. They are not random. They are part and parcel of the complex ecosystem.

(a) Olson was added to the ORNL ecology group to provide more mathematical and modeling capabilities.

TABLE 11.2. Body Burdens of Radionuclides for Muskrats Collected from the Oak Ridge National Laboratory Settling Basin, 1960 to 1961¹

Animal Number	Burden of Radionuclides (microcuries)					
	Cesium-137	Cobalt-60	Ruthenium-106	Zinc-65	Cerium-144	Strontium-90
<i>Gastrointestinal Tract with Contents</i>						
202	0.639	0.859	0.394	*	*	1.370
204	0.976	67.600	*	*	*	12.400
279	0.122	0.089	0.014	0.560	0.077	0.214
280	0.478	0.207	0.045	trace	0.285	0.174
<i>Residual carcass</i>						
303	3.710	0.098	*	0.053	*	13.800
304	1.140	0.122	*	0.193	*	8.370
379	0.312	0.071	0.152	0.274	0.116	8.790
380	2.040	0.094	0.450	0.029	0.054	6.540

¹Animals 202 and 204 collected August, 1960; animals 279 and 280 collected March, 1961.

*None detected.

Source: Reset from Kaye and Dunaway 1963. Reprinted with permission of Van Nostrand Reinhold Co., Inc., New York, copyright 1963.

It is somewhat surprising to find in the paper by Dunaway and Kaye (1963) that pathologic effects could not be demonstrated in the various mammalian forms collected. Chromosome aberrations *did* turn up in the insect larvae collected.

The importance of having such a program in a completely different geographical area from the Hanford site should be emphasized. The terrestrial programs at Hanford and, as we shall see later, at the NTS concerned desert environments. Radionuclide transfer paths might be quite different there from the moist forests of Tennessee. Even the Clinch River studies contrast sharply with those of the Columbia. The volumes of water and effluent are relatively small in the Clinch River system; plankton plays a more important role in radionuclide uptake. The system is warmer, slower moving, and more polluted, and the species inhabiting it are quite different in toto.

The environmental effort at Oak Ridge during the period of interest here was augmented considerably by the addition of the "Health Physics Reactor." This was placed in a wooded region and provided an unshielded source of neutrons and gamma rays for many purposes. The ecology group measured effects on the flora surrounding it and found much the same differential sensitivities of plants as the Brookhaven group had found with their large gamma-ray field (see section III D). Also, the ORNL group did much work under laboratory conditions on the effects of gamma irradiation in a variety of organisms. Details can be found in the summary report cited above (Auerbach and Schultz 1962); they are beyond the scope of this discussion since they involved only external radiation sources.

C. Savannah River Ecology Program

At the beginning of the decade of the 1950s, the AEC, with the support of Congress, the Joint Committee on Atomic Energy, and the military, decided that a second major production site for plutonium was needed along with the then highly classified radionuclides concerned with the fusion process. A site of about two hundred thousand acres was chosen along the Savannah River in South Carolina. Without the urgent schedules of the MED days, there was opportunity to do some preliminary ecological work before the plant was constructed and to take advantage of some unique opportunities. Some of the area had been under cultivation prior to the acquisition of the land by the government. Its gradual reversion to the wild state, i.e., the "old field phenomenon," plus the fact that several distinct geographical situations were involved, made the site of prime interest to ecologists. Furthermore, it would be largely closed to the public, so studies could be carried out in a protected environment.

An initial ecological study was made of the Savannah River by the Academy of Natural Sciences of Philadelphia. This provided base-line measurements of plants and animals in the river before plant construction and operation began. This work has continued, particularly by using diatoms, single-celled algae, as "markers" for the health of the river.

Also in 1951, the AEC made arrangements with Eugene Odum at the University of Georgia to begin an inventory-type ecological study of the entire area and to plan ecosystems research. There was, of course, no manmade radioactivity present since the plant was yet to be built. Dr. Odum, probably the dean of American ecologists, seized on the opportunity to have a protected outdoor laboratory for both experimental studies and observation of the succession of flora and fauna. He and three graduate students began by commuting from the University of Georgia in Athens and "conducted their research out of suitcases and an abandoned barn" (SREL 1979). Soon one of the better of the dwellings that had been vacated was pressed into use as a field station ("Bush House"). The operation was called the *Savannah River Ecology Laboratory*.

It was not until 1962, almost the end of what we are regarding as the early postwar years, that a more permanent facility was built, and full-time research staff were placed onsite. Dr. F. B. Colley was the first director. The close relationship with Eugene Odum and the University of Georgia continued.

The Savannah River work was perhaps the least single-minded of those we have reviewed thus far. The reactors produced large quantities of warm, even hot water, which could be used for studies of thermal stress. There were large quantities of tritium being emitted from the stacks. The usual radionuclides were in the waste water streams in controlled small quantities. The usual problems of waste disposal existed. A large lake and several ponds, which allowed progressive analysis of the interaction of a large nuclear facility and a fairly well-characterized environment, filled out the opportunities.

Work of particular pertinence to radionuclides included monitoring of the separations processes, waste disposal and reactor operations, and development of information on food chains in each of the several distinct environments. The effort went far beyond control purposes. Over forty thousand analyses were made each year on environmental samples of air; water in streams; underground water and drinking water; milk and other farm products; vegetation; animals and waterfowl; fish, crabs, and oysters; and algae and diatoms (Bebbington 1973).

A general overview of the extent and kind of environmental sampling utilized is shown in figure 11.5. At the risk of anticipating concepts we will take up in more detail further along, the summarized findings are shown in figure 11.6A and B.(a)

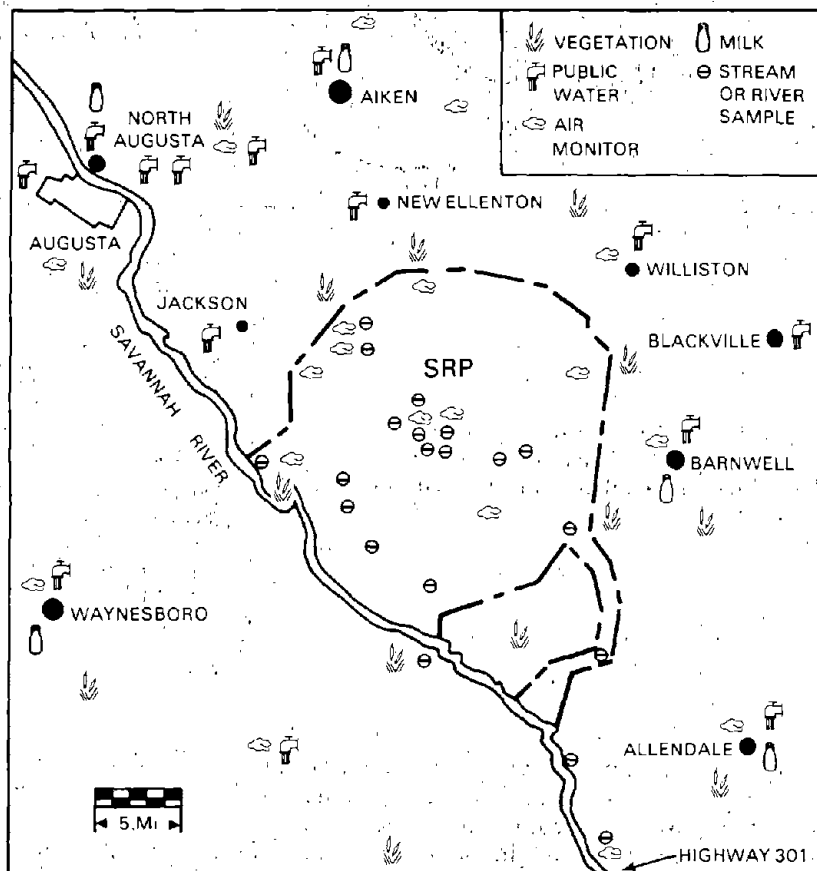


FIGURE 11.5. Environmental monitoring locations around the Savannah River Plant (SRP) on the South Carolina side of the Savannah River. For scale orientation, the SRP is about 20 miles east of Augusta, Georgia. (Redrawn from Bebbington 1973.)

These figures show the large amounts of tritium and noble gases in the operation of this facility. Compared to Hanford and Oak Ridge, this site had relatively more of these radionuclides. Since the biomedical problems of tritium were reviewed extensively in chapter 10, and we will need to add further environmental aspects in chapter 12 when we consider weapons tests, we will not

(a) Although these are from a 1973 document, the nature of the emissions has not changed very much since the time the plant opened.

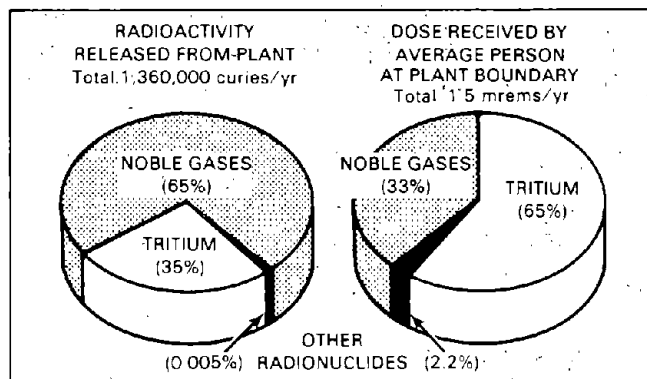
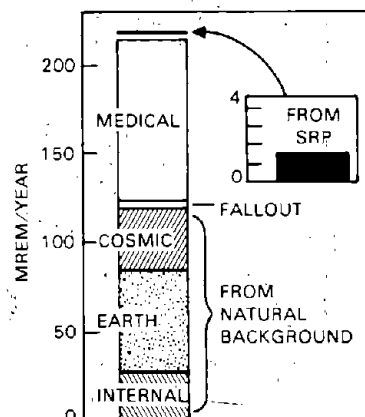


FIGURE 11.6A. Radio-nuclide releases and calculated doses from operations of Savannah River Plant (Redrawn from Bebbington 1973.)

FIGURE 11.6B. Radiation dose originating from Savannah River Plant for nearby resident compared to doses from other sources. (Redrawn from Bebbington 1973.)



review the subject in detail here except to point out that emissions of the more toxic radionuclides at such levels would, of course, be intolerable. It is fortunate that tritium and the noble gases are among the less toxic radionuclides.

Figure 11.6A also illustrates the impressive ability of the environment to dilute large quantities of relatively inert (chemically) substances. With releases of over a million curies per year of tritium and the noble gases, the average dose to a person at the plant boundary is only 1.5 mrem/yr.

The connection with the University of Georgia was formalized as an Institute of Radioecology, and it still continues.^(a) Most of the work involving radionuclides has borne primarily on assessment of releases, doses, etc. The more purely research aspects have concerned more classic ecology. A measure of the scope of interests and activities at the Savannah River-University of Georgia facility can be seen in the review given by Odum at the first Atoms for Peace Conference (Odum 1956). He emphasized the need to study whole communities of organisms and illustrated the types of work by such classic ecological methods as productivity of the organisms in a coral reef by measuring oxygen flow, the annual community turnover of biomass, measurements of trophic

(a) At the cutoff time for this chapter; see preface.

structure (i.e., the overall food chain) measurements of species structure, and the comparison of contaminated and noncontaminated areas. This was indeed classic ecology with one new variable introduced—radioactivity.

As a final commentary on the activities at these three major sites in the MED and early postwar years, we can look at table 11.3, taken from a paper by authors from all three laboratories and given at the second Atoms for Peace Conference (Brown et al. 1959). The figures concern experience with disposal of radioactive wastes.

TABLE 11.3. Comparison of Three Major Production Sites (liquid radioactive wastes)

	Cumulative Total Volume (liters)	Cumulative Total Gross β -Emitter Activity (curies)
Savannah River	5.0×10^8	$2.4 \times 10^{2*}$
Oak Ridge	2.6×10^7	1.0×10^5
Hanford	1.2×10^{10}	2.4×10^6

*Not including 2300 curies of ^{131}I .

Source: Reset from Brown et al. 1959, p. 556. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1959.

The cumulative figures are, of course, not strictly comparable because the sites had not been in operation for equal periods. They show, however, that the average activity^(a) is lowest at Savannah River, highest at Oak Ridge. They also emphasize the fact that waste disposal is and will be a much greater problem than day-by-day releases. The conclusions of this paper are premonitory of the enormous effort that was to be needed and is still needed on waste disposal problems. They are quoted below.

The problems associated with the disposal of high-level radioactive wastes are certainly large and serious. However, the problems associated with the low to intermediate level streams, bulking many times the volume of Savannah River high-level waste, are also of great importance. Even the essentially uncontaminated process cooling water cannot be released into many public waterways owing to its potentially significant radioisotope content. The experiences at Oak Ridge, Savannah River and Hanford point out means by which disposal may be accomplished but not without the assumption of an extensive and exhaustive research program and the grave responsibilities associated with that disposal. (Brown et al. 1959)

The net result of the MED and early postwar work at these three major sites was that releases of radioactive materials had been normally below the limits for detection of effects on man or the biosphere, but the enormous legacy of radioactivity awaiting safe disposal would require the best efforts of the future.

(a) In terms of concentration.

D. Other U.S. Activities in the Early Postwar Years

There were, of course, monitoring programs and some ecological studies around facilities other than the three major production sites discussed above. These include uranium ore processing and refining mills, the major AEC laboratory sites, and also many research projects mounted by universities with interests in ecological research. Although much of the activity concerns weapons fallout and will be detailed in chapter 12, we need to consider here those activities that were qualitatively like the larger ones already taken up.

1. Uranium Mills and Refineries

There were several uranium processing mills (concentration plants) located primarily in the West, not too far distant from the mines. These processed the uranium ore for removal of other radionuclides such as ^{226}Ra and the members of its decay series. In addition, there were many refineries located primarily in the East and Midwest. Many of these were dusty operations, and much attention was paid particularly through help from and direct measurements by the Health and Safety Laboratory (HASL) of the New York Operations Office of AEC to proper measurement and evaluation of airborne uranium dust and the exposure of workers and the immediately surrounding population. These operations have been alluded to in chapters 8 and 9.^(a) A succinct history of the uranium production chain and early occupational exposure experience is provided by Eisenbud (1975), also in the recent book by Whicker and Schultz (1982).

The principal environmental problems arose around the mill sites. These mills put aside the residues from the processes of concentrating uranium as "mill tailings." Millions of tons of such tailings had accumulated by the late 1950s. They contained several thousand curies of ^{226}Ra . Even though the tailings impoundments were partially stabilized and partially contained, it was only a matter of time before elevated radium concentrations began to appear in streams and in water supplies derived therefrom for drinking and irrigation. The first data appear to have been generated prior to some Congressional hearings in 1959. The most highly publicized, early case of radium contamination involved the Animas River in Colorado-New Mexico. This river provides drinking and irrigation water for Aztec and Farmington, New Mexico. The ^{226}Ra content of the river and drinking water was measured by USPHS officers and staff, primarily under the direction of E. C. Tsivoglou, whom we met in chapter 3 in connection with radon problems (Tsivoglou 1959; Tsivoglou et al. 1960), with a follow-up in the first Radioecology Symposium showing effects on biological fauna in the river (Anderson, Tsivoglou, and Shearer 1963).^(b)

The radium concentrations in the Animas River below Durango, Colorado, where the mill was located were markedly higher than above the mill. Indeed, consumers of untreated water would have received, had they used it, about 300% of the maximum permissible daily intake of radium on the basis of standards of the International Commission on Radiological Protection (ICRP) (chapter 16). The drinking water in Aztec and Farmington was at 170% and 140% of the

(a) The details appear in part in the two symposia on occupational health experience with uranium, viz., Energy Research and Development Administration (ERDA 1975) and HASL (1958).

(b) Tsivoglou was then working out of the Taft Sanitary Engineering Center of the USPHS in Cincinnati, while Anderson was at the PHS office in Dallas.

permissible daily intake, respectively (Eisenbud, 1973). All of these concentrations of radium were, when first measured, several hundred times the normal for these waters. It appeared that radium was entering from untreated liquid wastes at the mill and through run-off from the tailings during rainy periods. Unlike the situation described in chapter 3 for the uranium mines, the mills were an AEC responsibility, and steps were soon taken to correct the run-offs. By 1963, the radium content of the river was only about three times as high below as above the mill rather than several hundred times. However, as water standards for radium have gone downward (see chapter 16), the acceptability of the measures taken or even possible has gone down correspondingly. The problem is still with us.

In addition to water leakage from the tailings, additional problems were brewed by the release of radon gas and the transfer of dust by wind. Measurements were aided again by the New York Health and Safety Laboratory. As a result, the tailings sites have been covered with topsoil and plantings. The current situation is a great improvement, since the present radon values are well below the accepted limits for the public. Indeed, Whicker and Schultz (1982) consider the current hazard from these sites as small and easily managed.

A succinct and readable summary of how the mill tailings problem grew and affected one community, Grand Junction, Colorado, is given by Siek and Baird (1972) from the Colorado Department of Health. This discusses air and water pollution studies and then elaborates on the fact that mill tailings had been removed from the mill site and used for construction of houses, surfacing of roads, etc. There was a significant radon problem generated thereby. It also reviews the resulting indoor radon studies, the enactment of legislation regarding containment of uranium mill tailings, and the development of levels at which remedial action should be instituted.

Clearly, there is a population that in the years of our interest in this section received doses considerably larger than those at the major production sites, except for accidental releases. Unfortunately, the population is too small to support a viable epidemiologic study for determining effects of either the waterborne radium or other chemicals, or the radon in air. The only indication of biological effects came from the studies of Anderson, Tsivoglou, and Shearer (1963) and Tsivoglou et al. (1958) on the river organisms. There is no question that the bottom fauna in the Animas River from below the mill to at least the New Mexico state line were greatly reduced in number and that the food supply for fish in that stretch of the river was also reduced. Concentration factors (see preface and section VI) for radium in the biota ranged from one hundred to one thousand. Unfortunately, the mill effluents contain many chemically toxic substances as well as the radionuclides. Thus, the change in abundance of bottom fauna cannot be ascribed to any single factor. We can only speculate on the role of radium.

The refineries were not, in general, of much ecological importance during the years we are considering here. They were more contained operations and did not have a phenomenon like the tailings piles around the mills. Only in very recent years have they become of concern to environmentalists and stimulated research, as we will see in section V. By and large, the refineries were spared the problems of disposal of radium because they received a purified starting material for their operations.

When the process gets as far as fuel fabrication, environmental concerns become truly minimal. Only in the event of serious accidents (both uranium

and plutonium metal are pyrophoric), usually explosive reactions, does environmental contamination become of concern.^(a) The intrinsic value alone of the materials by this stage ensures strict containment in routine operations.

2. Reactors

We will postpone discussion of nuclear reactors in the United States to be able to consider the problems of modern reactors as a unit. Because of its landmark character, we will review the Windscale reactor incident in the United Kingdom in some detail in section III E.

3. Fuel Reprocessing Plants

As we have seen, the Hanford and Oak Ridge sites had facilities for fuel reprocessing. The Savannah River complex was added in the period we are calling the early postwar period. It had a large fuel processing capability. A plant at the Idaho Falls Nuclear Reactor Testing Station came soon thereafter. Also, there were privately owned reprocessing plants, but these came along in a later period.

The chief concern regarding environmental contamination around these facilities comes from the relatively enormous amounts of radioactivity that must be handled. Nevertheless, only the facilities integrated into the large production sites have been part of an integrated environmental and ecology program. The rest have had ample surveillance activities, but not work that would qualify as research for this volume. Eisenbud (1973) gives a clear review of some of the activities of and around fuel reprocessing plants, with special emphasis on a plant built under the aegis of New York State at West Valley, New York. This went into service in 1966, but there were many problems, financial and operational. With the decline of nuclear power activities, the facility is on a standby status.

4. Other U.S. Government Laboratories

Each of the major national laboratories had from some to considerable interest in environmental and ecological problems.

We have already reviewed the considerable interest at Argonne National Laboratory (ANL) in radium in natural waters (chapter 1). Later they became interested in actinide elements in the Great Lakes and in fallout problems. Also, the group mounted many laboratory investigations with ecological significance.

Brookhaven National Laboratory (BNL) has been a center for ecological research and work bearing on the environment almost since its founding. Its involvement with radioisotopes bears primarily on the fallout events in the Pacific and will be described in chapter 12. Its other major activity centered on the gamma field. This was a multicurie source of gamma photons placed in a large field with woods nearby. Much of our information on the relative radiosensitivity of plants, from primitive to complex, in a natural environment came out of the work of Sparrow and his colleagues at Brookhaven using this facility. In addition, the group has carried forth much basic laboratory research on lower organisms. We have met much of this in connection with specific radio-nuclides (e.g., tritium).

(a) Eisenbud (1973) describes a significant release of plutonium by explosion in a chemical processing plant at Oak Ridge in 1959. There have been other isolated releases, but these have been small compared to the operations.

We have already had many occasions to encounter the work of the AEC Health and Safety Laboratory. This laboratory supplied instrumentation and special services to the weapons testing operations, developed the worldwide network for gathering and measuring fallout, and studied fallout radionuclides in food and water, etc. Indeed, there were few aspects of environmental contamination with radioisotopes that HASL was not involved with. The staff was even able to mount research in its own right.

The Knolls Atomic Power Laboratory, the back-up for the Naval Reactor program, is reported by Kornberg and Davis (1966) to have done a small amount of environmental work on its releases of radioactive materials.

The Los Alamos Scientific Laboratory (LASL) has had programs to assess the movement of radionuclides, especially plutonium, in the canyons on the site used for waste disposal. However, its principal involvement with environmental concerns centered on the NTS and selected aspects of the work at the Pacific Proving Ground that involved the physicists at Los Alamos. In addition, there was laboratory work on lower organisms with applications to ecological problems.

The Puerto Rico Nuclear Center has a reactor and other facilities and cooperates with the University of Puerto Rico in a radioecological study of a rain forest (external radiation source). The group at Mayagüez has become considerably involved with marine ecology and the movement of radioisotopes in marine environments. Their work has not been site-oriented to a significant degree and appears in later chapters.

The U.S. Bureau of Commercial Fisheries at Beaufort, North Carolina, particularly T. R. Rice and his colleagues, has had both research and surveillance activities regarding contamination of the marine environment. This group has worked closely with other aquatic biology groups, particularly the one at Savannah River.

The Woods Hole Oceanographic Institution, not strictly a U.S. government installation, but subsisting almost entirely on governmental contracts, has been very active in research on radioisotopes in the marine environment. The work has been spearheaded by Vaughan T. Bowen.

An informative overview of the environmental surveillance activities at all AEC sites can be obtained from a series of annual reports entitled "Environmental Monitoring at Major U.S. Atomic Energy Commission Contractor Sites." A typical example is the one issued for the calendar year 1973 (AEC 1973a). Activities at twenty-eight sites are described in a more or less uniform format arranged in order of the operations offices. Some glimpses are given of new ideas, such as the use of the honeybee as a monitor for tritium at Los Alamos. (It was more reliable than the air monitors!) Each one has a section on dose to the public. Anyone wanting to see what measures were taken at the sites to protect the public and the environment can learn much detail (but not so much philosophy) from these documents.

The other major governmental participant (if we consider the Naval Reactor program as part of AEC) was the U.S. Public Health Service.

We have already seen that the PHS eventually took an active part in evaluation of uranium miners (chapter 3) and acted promptly in uranium mills (section III D, above). In addition to the team they sent to Hanford soon after the war, the PHS has also assisted with surveys on the Savannah River estuary and on the Clinch and Mohawk Rivers (Sobo and Bedrosian 1963). The largest involvement of the PHS has been through its regional laboratories and officer

assignments. Some of the early ones were temporary satellites of the Robert A. Taft Engineering Center in Cincinnati, e.g., the Environmental Health Center at Oak Ridge where Melvin Carter was assigned in 1951-1953 (Carter 1979). There were short-term assignments of PHS officers to the early weapons test organizations, such as Crossroads and the Nevada Tests. Later the assignments came from the regional centers.

The regional centers of the PHS all conducted research bearing on environmental concerns. Indeed, we have seen some of the research, especially on noble gases and related areas in previous chapters. None was any more intimately involved with ecological and environmental problems than the Southwestern Regional Laboratory in Las Vegas, Nevada. This group was involved with the Pacific tests, as were other PHS personnel, and was very active, especially in the offsite monitoring, at the NTS. The three regional laboratories (Southwestern; Las Vegas; Northeastern, Winchester, Massachusetts; and Southeastern, Montgomery, Alabama) plus the Robert A. Taft Center and an occasional recruit from the National Institutes of Health (e.g., H. L. Andrews and F. Smith; see chapter 12) resulted in a diffuse, but considerable involvement of the U.S. PHS in most aspects of the environmental and ecological problems around the many production sites^(a) and in the weapons testing activities. As we have seen, this included several independent teams that sort of "double-checked" the findings of the large contractors. This author can find no reports that they differed in any substantive ways. Yet, the skeptical should have taken some comfort in having an independent agency of the U.S. government totally dedicated to health problems and with no possible conflict of interest in meeting test schedules or getting weapons data make confirmatory surveys and report comparable results. We will save the rest for chapter 12.

5. The Universities

Nearly every major university in the United States became involved directly or indirectly with environmental problems of radioactivity through work connected with fallout. The same was true, but to a lesser degree, in other parts of the world. A few U.S. institutions, especially ones with large AEC contracts, devoted major efforts to broad aspects of radioecology.

We have already mentioned the deep involvement and excellent work of the fisheries laboratory at the University of Washington and the close ties between the Savannah River Plant and the University of Georgia (sections II A and C).

The University of California system had active surveillance programs around all of its large installations. However, of greatest interest to our purposes are the research enterprises developed. Outstanding among these are the Scripps Institution of Oceanography, part of the University of California at San Diego, and the University of California at Los Angeles (UCLA). As a major center for oceanography, it was natural that the Scripps Institution would become deeply involved in the behavior of radioisotopes in the marine environment and in possible biological effects as a result of the problems of fallout and of waste

(a) A handy manual on routine surveillance of radioactivity around nuclear facilities was issued in 1966 under the aegis of the Division of Radiological Health (PHS 1966). This covers surveillance of air, food, water, biota, soils, precipitation, and in-vivo measurements of people.

disposal. The Scripps group participated very actively in the fallout surveys in the Pacific and mounted experimental work both in the field and in the laboratory. Scripps personnel played key roles in the development of National Academy of Sciences-National Research Council (NAS-NRC) reports on the effects of atomic radiation on oceanography and fisheries already cited.

The involvement of UCLA was primarily through its Atomic Energy Project. Stafford Warren, who went to UCLA at the end of the war as dean of the new Medical School, kept his interests in atomic energy and in environmental contamination problems alive through the project. Indeed, a major portion of its resources and personnel were directed to and still are at the NTS, and they were deeply involved in all biomedical aspects of the Pacific tests. Naturally, a considerable amount of laboratory research was mounted to check out various ideas arising from the findings in the field (chapter 13).

Some work on terrestrial radioecology was carried out on the Davis campus of the University of California. Most of that effort, however, was in the long-term laboratory animal studies discussed in chapter 8.^(a)

Colorado State University at Fort Collins has long had a unique capability in radiobiology extending from a large beagle dog experiment involving external radiation through cellular and molecular radiobiology to broad interests in radioecology. Through use of special sites in the Colorado Rockies as well as experiments on the campus, they have been involved with many studies, from local events to worldwide contamination from fallout. Their work has not been site-specific to Fort Collins. Ward Whicker, whose book with Vincent Schultz we have already mentioned several times, has his headquarters at Colorado State. Note also that this was the institution that hosted the first formal symposium in radioecology (section IV).^(b)

Emory University in Atlanta, Georgia, developed a strong radioecology program built around a reactor operated by Lockheed Aircraft Corporation for studies of shielding. This was a mixed neutron and gamma radiation field. The Emory group did not enter the arena of radioisotopes in the environment.

The University of Michigan, Michigan State, and the University of Minnesota have had interests in radioecology, but we will not be able to pinpoint their work beyond sponsorship of symposia, etc. (section IV).

Finally, in this brief listing of universities involved with radioecology in the decade or so after World War II, we should mention New York University, even though we have already seen their work in other fields. Through its Institute of Environmental Medicine (originally Occupational and Environmental Medicine) with facilities at Sterling Forest about fifty miles north of New York City, New York University has kept many programs active that bear on radioecology. Some of these represent a carry-over of the interests of Merrill Eisenbud from his experiences as director of the New York Operations Office of AEC. They include studies of high radiation background areas of terrestrial origin in Brazil

(a) The Lawrence Livermore Laboratory of the University of California had much of its biomedical program built around environmental contamination problems. This developed, however, in the years beyond those under discussion in this section.

(b) The University of Colorado at Boulder was involved in many aspects of fallout work through its Institute of Arctic and Alpine Research.

and India,^(a) ecological studies of the Hudson River estuary, with special emphasis on the Indian Point reactor, and much work on radium and the actinides in natural and manmade settings. They had considerable involvement with the characterization and measurement of fallout. Their work in pulmonary toxicology has already been reviewed (chapter 9). Later they expanded into the area of marine systems. The work most cogent to this chapter, however, is that concerning the Hudson River estuary. We will examine it briefly in a subsequent section.

Many other university organizations have been involved with radioecology to some degree. The listing above makes no claim to being complete. However, it does enumerate those groups we will have most occasion to cite directly or indirectly in subsequent pages of this chapter and later chapters.

E. Work Abroad

The field of radioecology was primarily a U.S. concern during the early work at Hanford and Oak Ridge. With development of reactors very early postwar in the United Kingdom and the USSR, interest in environmental contamination developed quickly. Russian work went early to problems of the aquatic environment. Indeed, enough work had been done in the USSR to provide about sixteen pages of Russian titles in the fifties and early sixties in a very useful book by Polikarpov (1966). This book is also an excellent review of work in other countries, especially the United Kingdom and United States (approximately eighteen pages of references to the non-Russian literature), but including Canada, Finland, France, Germany, Italy, Japan, Monaco, and Sweden as well.

The work abroad, like that in the United States, involves both external radiation sources and radionuclides, especially, of course, those in fallout. There is not so much of it specific to production sites, the subject of this chapter, in the early postwar years except in the U.K. work. The Polikarpov book is about equally devoted to data resulting from generic site measurements (but not specific sites), fallout measurements, and controlled laboratory investigations. Other references to Soviet work can be found in the bibliography to chapter 1 of the book by Whicker and Schultz (1982).

1. Canada

Site-specific research and surveillance has been carried along regularly by the Canadian Atomic Energy Authority. The most research oriented has been around the Chalk River installation of Atomic Energy of Canada, Ltd. The earlier literature is, however, rather sparse, at least in sources available to this author.

An early report was part of a summer symposium on the role of atomic energy in agricultural research held at Oak Ridge in August 1952 (Comar and Hood 1953).^(b) It was summarized in the Newsletter of the Oak Ridge Institute

(a) The essence of the work in Brazil has now come to fruition. At the 1985 annual meeting of the National Council on Radiation Protection and Measurements (NCRP), Eisenbud delivered an eloquent summary that raised questions about the need for some aspects of the billion-dollar effort now going into high-level radioactive waste disposal. Despite a potentially large source of radioactivity (thorium series isotopes) contained in a mountain, essentially none was found in surface or ground water. In Eisenbud's review, he states that the materials are extremely firmly fixed chemically and will remain so for eons.

(b) The Canadian work is outlined on page 482.

for Nuclear Studies, September 1952. R. R. Langford and F. H. Rigler discussed organisms and bottom deposits in the Ottawa River above and below the Chalk River plant. They showed wide variety in the rate and total accumulation of radionuclides. The accumulation increased in the approximate order: rooted plants, epiphytic plants, bottom insects (burrowing less than surface bottom insects), small clams, minnows, and small fish. There was seasonal variation in the accumulation as a function of water temperature—based, of course, upon fluctuations in metabolic rate of the organisms.

At the first radioecology symposium, Ophel (1963) presented a detailed discussion of the fate of radiostrontium in Perch Lake, Ontario, which is situated within the Chalk River establishment.^(a) A scan of the results can be gained from figure 11.7.

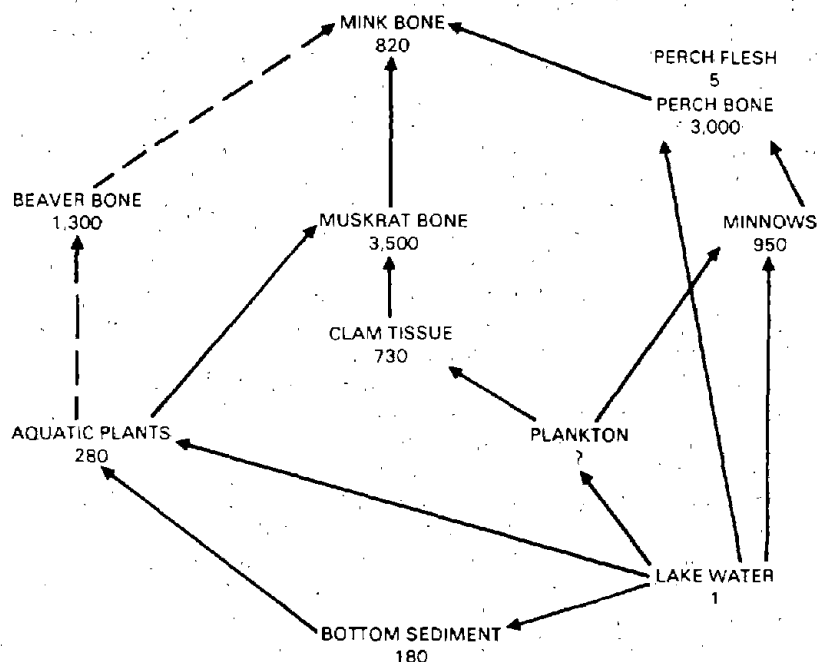


FIGURE 11.7. Average concentration factors* for ^{90}Sr in Perch Lake food web. (Redrawn from Ophel 1963. Reprinted with permission of Van Nostrand Reinhold Co., Inc., copyright 1963.)

$$* = \frac{\text{Concentration in Aquatic Organisms}}{\text{Concentration in Aqueous Medium}}$$

Obviously, the concentration factor for strontium is much greater for bone than for flesh as would be expected, but there are significant differences between species. (Fortunately, we do not eat the bones of any of these species.) But note that aquatic plants can be higher than perch flesh and that there is a considerable amount deposited in bottom sediment.

(a) This lake received dissolved radionuclides from adjacent liquid waste disposal areas beginning in late 1955.

A large effort took place at Chalk River in connection with their contamination accident. However, that was primarily within the building and is not pertinent to the present discussion.

2. The United Kingdom

The first British production reactors went into operation in a remarkably short time after the end of World War II, i.e., 1950–1951. (Licensing was not the hassle then that it is now!) The location was Windscale on the Irish Sea in north-western England. There were two air-cooled graphite-moderated natural uranium reactors used for the production of plutonium and an associated chemical processing facility. Waste from this fuel processing facility has been discharged into the Irish Sea for many years. First there was an experimental discharge of about 10,000 Ci of radioactive effluents over a period of about six months in 1952 (Eisenbud 1973). When it was found that the activity of the water was from 0.01 to 0.1 $\mu\text{Ci/ml}$, it was deemed safe to continue the practice, even increase the annual releases. The principal radionuclide discharged was ^{106}Ru .

The U.K. Atomic Energy Authority kept very close tabs on the contamination of the sand, the silt, the seaweed, and the fish, and by the time of the second Atoms for Peace Conference in Geneva they were ready to make international disclosure of their findings (Dunster 1958). They had studied the dietary habits of local residents and determined that one species of fish and a seaweed used in preparation of a local bread (laverbread) were the critical pathways for human exposure. They designed some limits, found that, of the nuclides being discharged, ^{106}Ru was the limiting one in the seaweed and determined that a discharge rate of 7,000 Ci per month would be acceptable.^(a) Eisenbud (1973) points out that, if the laverbread pathway had not existed, fish would have been the critical pathway, and the permissible releases could have been much higher. In typical British fashion, there was no thought at all of trying to change the dietary habits that had existed in the population for generations. Public relations around the plant were tenuous enough without that.

These discharge rates for "low-level" radioactive waste seem high, especially when compared to those for total radioactive waste from three U.S. sites shown in table 11.3. We must remember, however, that these figures are very site-specific. Eisenbud (1973) gives a tabular survey of the isotopic composition of Windscale wastes derived from work of Howells (1966). The Dunster paper already cited expands into use of the Windscale information for "safe discharges" into other coastal waters.

There was, of course, a terrestrial survey and technological assessment. The graphite reactor puts out radioactive noble gases, radioiodine, and other fission products in very small quantities with the cooling air. The terrestrial survey data were discussed publicly by the British even before the aqueous discharge data quoted above. Fair and McLean (1956) describe use of mobile laboratories to do alpha, beta, and gamma surveys of an area with a radius of about twenty miles of the Windscale Works before the plant was constructed. As with many background surveys, the local variations were large. No single figure could be assigned to any one point. However, the influence of many meteorological conditions was pinpointed.

(a) Total beta activity could have been 20,000 Ci per month, while any sizeable amounts of ^{90}Sr or plutonium isotopes would have reduced the limit drastically. Work on the Irish Sea is still going on.

The same routines were conducted after the plant went into operation. The results were comparable to the old air-cooled graphite reactors at Brookhaven and Oak Ridge in the United States. Chamberlain et al. (1956) from the Atomic Energy Research Establishment at Harwell published a careful analysis of tolerable levels of ^{131}I , ^{90}Sr , and ^{89}Sr in food chains. This analysis included the scenario of daily depositions, intermittent deposition, or total deposition of fission products in soil in which crops were to be grown and allowable amounts in herbage versus milk. An interesting conclusion was that hazard from ^{131}I from herbage would lead to permissible discharges a factor of one thousand lower than the hazard from breathing radioiodine (see chapter 10). Permissible amounts of ^{131}I and ^{89}Sr were comparable in this system.

This routine surveillance at Windscale became far from routine in October 1957. Release of stored neutron energy in the graphite core of Reactor Number One was excessive in certain areas, but went undetected because of insufficient instrumentation to cover all parts of the core. Metallic uranium and graphite began to react with air and many fuel elements burned over a period of four days. The incident is described graphically by Eisenbud (1973, pp. 411-412); by Dunster, Howells, and Templeton (1958);^(a) and by Denham and Waite (1982). The isotopes released to the environment were ^{131}I , 20,000 Ci; ^{137}Cs , 600 Ci; ^{89}Sr , 80 Ci; and ^{90}Sr , 9 Ci.^(b) Presumably the preponderance of iodine was due to its greater volatility.

The survey activities included estimates of the external radiation hazard, inhalation hazards, and hazards from ingestion of contaminated food and water. It was soon clear that the first two were negligible compared to the third. A milk sampling network was quickly established. By recruiting personnel and equipment from places like Harwell, Aldermaston, Woolwick, etc., and devising a quick method of measurement, they were able to analyze several hundred milk samples per day. The highest activity reading was $1.4 \mu\text{Ci}/\text{mL}$ obtained from a farm about ten miles downwind from the reactor and about four hundred feet higher. The activity/time relationships for the iodine in milk are shown in figure 11.8, taken from the paper by Dunster, Howells, and Templeton.

It was soon realized that use of milk from some local farms would have to be stopped. Very quickly, a level for restriction was decided upon, viz., a level in milk such that normal intake would result in a dose of no more than 20 rad to the thyroid.^(c) The milkshed survey covered about two-hundred square miles, which are mapped by Dunster, Howells, and Templeton (1958). Milk deliveries were controlled or stopped throughout this area.

(a) The review by Dunster and colleagues was at the second Atoms for Peace Conference held in 1958. It was the longest published paper in the proceedings, and it tells the complete story of not only the accident itself, but the countermeasures taken, measures made, and the way in which the entire British nuclear establishment acted almost as a single agency and as if they had been practicing for years for such an incident.

(b) Howells (1969) cites the release also of 21,000 Ci of ^{132}Te , an isotope that would behave much like iodine.

(c) This was derived from the knowledge that 200-rad had sometimes produced thyroid cancer in children. Since children would be the most vulnerable individuals, a level of one-tenth this amount was chosen as the cutoff point. This came out to be $0.15 \mu\text{Ci } ^{131}\text{I}/\text{L}$ of milk. The decision was checked and assented to by the Ministry of Agriculture, Fisheries and Food, which has responsibilities in the United Kingdom akin to the original responsibilities of the Public Health Service in the United States.

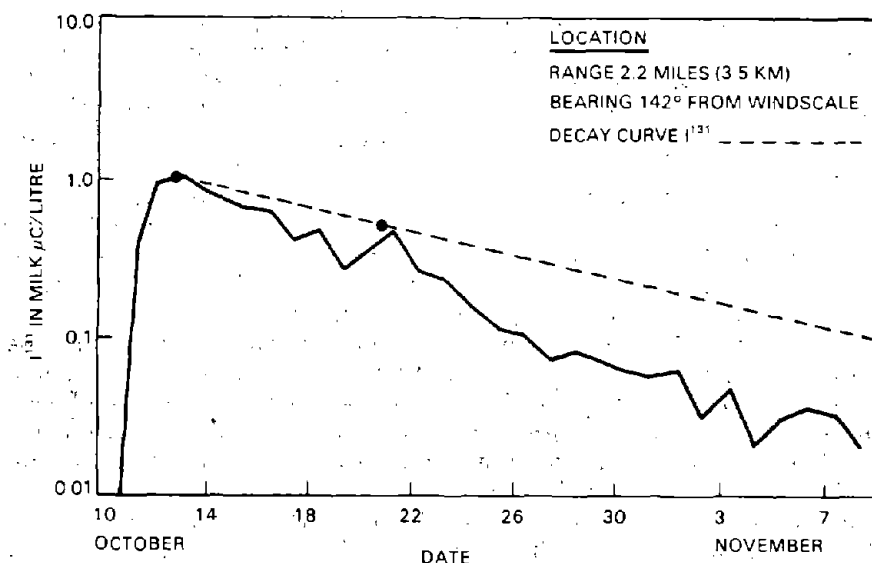


FIGURE 11.8. Decay curve of I^{131} in milk near the Windscale Works of the United Kingdom. Note the disappearance is more rapid than simple radioactive decay would predict. (Redrawn from Dunster, Howells, and Templeton 1958. Reprinted with permission of Pergamon Press, Ltd., copyright 1958.)

Air and ground fallout samples were measured at much greater distances from the plant, even in Northern Ireland, the Isle of Man, and into southern England. There was a well-defined plume, since the wind was relatively constant in direction, except for one or two hiatuses.

Iodine-131 concentrations were measured in drinking water, in human thyroids, in and on vegetation, and in soil. As soon as analytical facilities and personnel permitted, concentrations of the strontium isotopes were also measured in detail to be sure that the initial preponderance of iodine had continued. None of the levels of contamination found were high enough to cause undue concern at the time, although the highest dose to a child's thyroid was 16 rad and the highest to an adult was 9.5 rad.

Only the milk supply was considered contaminated enough to require interdiction. Areas were released to normal usage as the concentrations of iodine in milk declined. Some areas were released relatively soon. The last area to be released was a coastal region extending about twelve miles southward in the direction of the main plume. Even this was released before the end of November. (Note that enough strontium analyses had been done to assure that when the iodine was down the milk was safe insofar as other radionuclides were concerned.)

They even went beyond pure surveillance into research, which concerned the correlations between gamma radiation levels and iodine concentration in milk, between iodine in grass and in milk, and between strontium in grass and in milk.

The variability of sampling and measurements on ground and of grass was sufficient to make it clear that nothing could substitute for the measurement of milk itself. This was true also for other foodstuffs.

An interesting sidelight on the Windscale incident is that local unskilled inhabitants were drawn in very early to help gather samples and even do surveys of ground activity. Even though the incident was hardly welcomed by the inhabitants of the area, they seemed very willing to lend a hand in determining whether or not a health hazard existed. This was not very long after the end of World War II, and the British seemed still to have the spirit of helping each other that had brought them through the war.

There is no question that the details of the handling of the Windscale episode provided a primer for all other emergency management plans for radionuclide contamination of the environment from nuclear facilities. Even though many things would have been done differently with experience, the rapidity of the response, the quick decisions on allowable levels, not only for iodine but for strontium and other radionuclides, and the competence of all the scientists who took part from near and far rate kudos.^(a) Also, this incident underlined the need for extensive advance planning and laid the groundwork for much of the new work around reactor sites and planned reactor sites on both sides of the Atlantic.

The Fisheries Radiobiological Laboratory of the U.K. Ministry of Agriculture, Fisheries and Food, located at Lowestoft, Suffolk, which took an active part in the Windscale incident, appears to have monitored the aquatic environment of all major nuclear energy facilities in the United Kingdom on a regular basis. Mitchell (1969) gives a useful summary of their approaches and practices and assesses the radiation doses received by various critical groups in the population.

Much more could be said about U.K. practices and research in the field of environmental contamination. However, these relatively early studies should establish that the United Kingdom gained experience rapidly, even if not necessarily by design.

The Windscale incident would not go away even after the extensive reports cited above. In 1982 and 1983, there were two reports for the National Radiological Protection Board that added new information (Crick and Linsley 1982, 1983). The first report reviewed all of the data released and concluded that the total population dose ("collective effective dose equivalent," a relative of the effective dose equivalent, but integrated to infinity) was 1.2×10^3 man-sieverts and that most of the collective dose came from the ingestion of contaminated milk. It was also concluded that the banning of milk consumption in the Windscale area "saved" approximately 3.5×10^3 man-sieverts of potential exposure. These doses were calculated to be comparable to one or two weeks of exposure to natural background radiation.

The story changes some in the second report. By adding in the contribution from previously unpublished data on other radionuclides, particularly ^{210}Po , and isotopes of plutonium, the collective effective dose equivalent was increased to 2.0×10^3 man-sieverts. This was considered to be within the range of uncertainty of the earlier estimate and still not of obvious health significance on the average. However, the fact that new information could appear so long after the incident attests to the complexity of the gathering and handling of data for environmental contaminants.

(a) Probably much was gained by the directness of the operation and publication in all media of the results. The scientific publications are summarized by Howells (1969).

Further and generalized detail is seen in the inquiry stimulated by the application of British Nuclear Fuels Limited to develop a reprocessing plant for irradiated oxide fuels and various support services (Parker 1978).

3. Others

Most of the work from Europe and Asia during the period of our concern in this section is not site-specific. The large literature from the USSR concerns general problems of aquatic radioecology, worker and population exposure standards, or, later, fallout measurements, and it is more appropriate to other sections of this and later chapters. Finland, Sweden, and other north European countries published work on terrestrial and marine contamination problems. The work can be seen in the various symposia that we will cite in section IV. Investigations in Japan have tended toward fairly general discussions and measurements during the period of our interest here and are not site-specific except for in-house documents concerning their developing facilities. Again, much of it applies to fallout problems and measurements.

A site-specific discussion of concentrations of elements in fish and aquatic plants in three rivers in West Germany was presented by Feldt (1971).^(a) The three rivers were the Ems, the Weser, and the Elbe, each of which had or was about to get power reactors of the boiling-water type. The investigation centered on the interesting question of how to limit effluents in each river so that maximum permissible concentrations or above would not occur in the North Sea into which they discharged. The choice of biological indicators and probable critical pathways led to the following conclusions on the measurements and their order or priority:

1. measurement of water by direct gamma spectroscopy
2. measurement of bottom activity
3. measurement of fish and plants to determine effects if any
4. measurement of radioactivity in mussels of the estuary

The priority was based on the fact that steps 1 through 3 could be carried out on the spot, more or less.

While many other reports have addressed this general problem of the additivity of radioactivity from several sites, this one is an especially readable and clear delineation of the thinking that can be applied.

IV. Radioecology Comes of Age

The decades of the 1960s and 1970s saw the field of environmental aspects of nuclear energy grow from specialized research around three major production sites in the United States to a fully accepted specialty in the atomic energy field and in ecology. The term radioecology or radiation ecology came into use independently and simultaneously in the United States and the Soviet Union (Whicker and Schultz 1982, Vol. I). Since much of the work on such subjects, as the transport of radionuclides, concentration factors, and the like were somewhat foreign to classical ecology, there were some individuals who objected to

(a) While dated later than the nominal period we are reviewing here, the work was done over many years and thus extends back into the 1960s.

the terminology. However, it soon became established and used. A descriptive outline of the field was given in the preface to these chapters.^(a)

In 1955, the NAS-NRC Committee on the Effects of Atomic Radiation on Oceanography and Fisheries issued a landmark report (NAS-NRC 1957) with the title the same as the name of the committee. This sounded an authoritative warning regarding the dumping of radioisotopes into the marine environment and set forth the gaps in our knowledge and the researches needed. When the Academy later prepared its series of reports called *Biological Effects of Atomic Radiation*, there was a further exposition on oceanography and fisheries plus one on disposal of radioactive wastes, on agriculture and food, and on meteorology. These were issued in 1960 (NAS-NRC 1960).^(b) Other NAS-NRC reports on these problems are listed later in this section.

Also in 1960, the symposium already mentioned on radioisotopes in the biosphere (Caldecott and Snyder 1960) was held at the University of Minnesota. This drew much discussion of radioisotopes in soils and plants, effects on genetic and somatic processes, toxicity of radionuclides, etc. It included a section called "Radioisotopes and Environmental Circumstances" in which the papers by Bustad and by Kornberg cited in the previous section were presented. The subject matter in toto for these endeavors was much broader than that encompassed by the definition of radioecology given earlier. Could radioecology by itself command enough interest and be coherent enough to support a major symposium entitled "Radioecology"? As we have seen, through references already made, the people at Colorado State University Institute of Environmental Biology in Fort Collins decided to organize a national symposium and see. The symposium was scheduled for September 1961. There was an overwhelming response. Almost ninety papers were accepted for the program, plus a panel discussion on education and research training needs in the field. Over one hundred participants materialized. There was much concern among the organizers as to whether or not so large a meeting would be successful. Would the papers have enough in common to keep interest up for the necessary five days? Would they be of high enough quality? The symposium was an immense success. The papers were of high caliber and the enthusiasm of the participants for their fledgling field universal. The volume was edited by Schultz and Klément (1963). Since it is a classic marking the real birth of radioecology as a broad discipline in the United States, the table of contents is shown as note 1 at the end of this chapter.

A second national symposium was held at Ann Arbor, Michigan, in May 1967 (Nelson and Evans 1969). This had sponsorship of the Ecological Society of America as well as the AEC and the University of Michigan. This one also drew ninety papers and included a presentation by John Wolfe, director of the environment section of AEC on retrospection and future. A few of the speakers came from countries other than the United States, but not many. The symposium included, in addition to a plenary session, sessions on population and community responses to radiation; individual and species responses; radionuclide cycling in freshwater organisms and environments, in marine organisms

(a) The maturation of the field was aided considerably by the several IAEA symposia cited on p. 816, as well as IAEA 1967, 1974.

(b) A later National Academy of Sciences-National Research Council Report confirmed and extended the ideas put forth in 1957 and 1960. The introduction by Allyn Seymour is particularly recommended (Seymour 1971).

and environments, and in terrestrial organisms and environments. It was, if anything, even more cohesive than the first symposium.

In 1971, a third national symposium called "Radionuclides in Ecosystems" was held at Oak Ridge (Nelson 1971). This one required two volumes for its publication. In addition to titles similar to those listed for the second symposium, there were sessions on thermal effects, modeling, and effects on plants and plant communities.^(a) There were even some discussions of transuranic problems that came to a head in the mid-1970s (sections V and VI).

There is no doubt that these three national symposia did much to consolidate the ideas and research protocols for the new field in the United States. They also provide such a complete and handy entrance to the literature that we can be content to describe primarily the general trends and key findings when we discuss these decades in the following section of this chapter.

There was a fourth national symposium held in 1975. It was under the auspices of Oregon State University at Corvallis, Oregon, and carried the title "Radioecology and Energy Resources" (Cushing 1976). It represents, to a degree, the merging of interests in radiation sources and radiation problems with other forms of energy generation.

Obviously, these symposia were not the only forces that contributed to the maturation of radioecology in the United States. There were hearings on fallout and on industrial waste disposal before the Joint Committee on Atomic Energy. In 1963, Merrill Eisenbud produced the first edition of his succinct and enormously useful book *Environmental Radioactivity* (Eisenbud 1963). Also in 1963, a conference on the Ecological Effects of Nuclear War was held at Brookhaven (Woodwell 1965). In 1965, one of the Hanford biology symposia, which was international in scope, considered "Radiation and Terrestrial Ecosystems" (Hungate 1965). In 1970, the American Chemical Society sponsored a symposium on "Radioisotopes in the Environment" (American Chemical Society 1970). This emphasized chemistry more than biology but considered many processes basic to the understanding of radioisotope behavior. Also in 1970, a symposium at the University of Minnesota on Nuclear Power and the Public (Foreman 1970), and a similar enterprise at the University of Wisconsin entitled "Student Conference on Nuclear Power and the Environment" (Carbon and Houlberg 1970) appeared. These both had sections devoted to environmental problems. In 1971, Eugene Odum wrote a chapter entitled "Radiation Ecology" in his much-used textbook *Fundamentals of Ecology* (Odum 1971).

The U.S. NAS-NRC had several committees active in the field of radioecology during this period. Their reports are, to a degree, basic to this and each of the following three chapters and will be quoted in some detail where appropriate. However, a formal listing at this point in our discussion may be helpful. The reports, including shorthand designation, are listed below.^(b)

1. NAS-NRC Report #551, *The Effects of Atomic Radiation on Oceanography and Fisheries* (The Revelle Report), 1957
2. NAS-NRC Report #655, *Radioactive Waste Disposal into Atlantic and Gulf Waters* (The Carritt Report), 1959

(a) Plants had, of course, been included in the other symposia but not under a special title.

(b) The author is indebted to Dr. Allyn Seymour, University of Washington, for helping provide this information.

3. NAS-NRC Report #658, *Consideration of the Disposal of Radioactive Wastes from Nuclear Powered Ships into the Marine Environment* (The Pritchard Report), 1959
4. NAS-NRC Report #985, *Disposal of Low-Level Radioactive Waste into Pacific Coastal Waters* (The Isaacs Report), 1962
5. NAS-NRC Report (no number); *Radioactivity in the Marine Environment* (The Rime Report), 1971

Finally, we can cite a 588-page bibliography on ecological aspects of the nuclear age prepared by the AEC and issued in 1972 (Schultz and Whicker 1972). Need we say more except to remind the reader that these same authors produced the two-volume book entitled *Radioecology: Nuclear Energy and the Environment* (Whicker and Schultz 1982)?

The international scene was comparably active. The emergence of reports from the classified literature to presentation at the Atoms for Peace Conferences has already been described. The first report of the United Nations Committee on the Biological Effects of Atomic Radiation (UNSCEAR) in 1962 carried a section on environmental aspects. The International Atomic Energy Agency (IAEA) in Vienna ran a continuing series of seminars, symposia, and reports beginning in 1960 and continuing to the present. Some of these are:^(a)

- Disposal of Radioactive Waste*, 1960
- Disposal of Radioactive Wastes in Fresh Water*, 1963
- Disposal of Radioactive Wastes into Seas, Oceans and Surface Waters*, 1966
- Practices in the Treatment of Low- and Intermediate-Level Radioactive Wastes*, 1966
- Disposal of Radioactive Wastes into the Ground*, 1967
- Management of Radioactive Wastes at Nuclear Power Plants*, 1968
- Environmental Contamination by Radioactive Materials*, 1969
- Environmental Aspects of Nuclear Power Stations*, 1970
- Population Dose Evaluation and Standards for Man and His Environment*, 1974
- Impacts of Nuclear Releases into the Aquatic Environment*, 1975
- Transuranic Nuclides in the Environment*, 1976
- Effects of Ionizing Radiation on Aquatic Organisms and Ecosystems*, 1976
- Biological Implications of Radionuclides Released from Nuclear Industries*, 1979
- Behavior of Tritium in the Environment*, 1979

The above list includes many quite large volumes. Thus, the amount of published work from IAEA alone is enough to establish radioecology as a very active field on the international scene.

An activity very nearly like the several American symposia occurred in Stockholm in 1966. Under the title *Radioecological Concentration Processes*, an international group filled 1,040 pages on this subject alone (Åberg and Hungate 1967).

For a field that started as highly classified work around Hanford and Oak Ridge, the above catalogue of American and international studies is most impressive. We can conclude beyond any doubt that radioecology has "come of age." Yet, the complexity of the environment and of ecosystems still leaves many questions unanswered. We devote the balance of this chapter to setting down the primary conclusions that have emerged and to reviewing relatively recent and current trends and some of the questions for the future. More will appear in later chapters.

(a) The full reference for each of these is given in the bibliography for this chapter.

V. The Later Years Around the Production Sites

In this section, we will attempt to summarize the major findings from the work, particularly in the United States, at the sites described as well as work along new lines and at new institutions.

The institutions named earlier were joined by others. A major addition was the biomedical program of the Lawrence Livermore Laboratory of the University of California. Starting early as a weapons-oriented laboratory, in later years it mounted a biomedical program with considerable environmental orientation. This was particularly concerned with a major outgrowth from the Atoms for Peace movement called Project Plowshare (chapter 14). Much of it concerns the Pacific Proving Ground and NTS, but their methodologies—particularly some aspects of their extensive meteorological effort—applied to work oriented around production sites as well.

In addition to those mentioned earlier, a major role in the oceanographic aspects was taken by Oregon State University and the Woods Hole Oceanographic Institute and their oceanographic vessels.

A. Generalizations

One of the first hopes of the radioecology enterprise as it bore on radionuclides was to describe the environmental behavior of each major group. When the work began, variability was so great that the hope for generalizations was considerably dampened. Fortunately, careful examination of the influence of physical factors such as climate and topography; chemical factors such as the inherent chemistry of the radionuclide and the nature of the ligands with which it might combine; the colloid and surface chemistry of the milieu, and the presence or absence of competing elements, the ecosystem properties, and the inherent characteristics of the biota involved did much to sort out the apparent confusion and randomness. Thus, by the 1980s, Whicker and Schultz (1982) were able to summarize the environmental behavior of specific groups of radionuclides and of key members of each group. This was developed from the world's literature and based especially on a series of reviews, which is given as note 2 to this chapter. They consider the nonmetals, light metals, heavy metals, noble gases, rare earths, and the actinides (Whicker and Schultz 1982, pp. 147-162). A very satisfactory overview can be developed from this compendium.

To make our cup really full, Whicker and Schultz got together a summary table of the ecological behavior of the important radionuclides in each category above. This is reproduced herewith as table 11.4. Some general patterns of behavior can be drawn from summaries like that given in table 11.4. The elements in the nonmetals category are all isotopes of essential nutrients. They are, therefore, readily assimilated and transported through food chains. Most of the light metal group are analogous (but not identical) to calcium or potassium and behave roughly like their analog. They, too, pass readily through food chains. The noble gases are, of course, unique and have essentially no nutrient analogs. They pass readily throughout the environment wherever substances in gaseous form can penetrate. The heavy metal group is much more varied, and behavior is less predictable and more dependent on chemical form and mode of biological exposure. Most heavy metals tend to deposit eventually in the sediments of aqueous systems or in soils. The rare earths of interest to us are generally poorly absorbed and poorly transported, as are the actinides.

TABLE 11.4. General Ecological Properties of Selected Radionuclides[illegible]

TABLE 11.4. Continued

Radionuclide <i>($T_{1/2}$)</i>	Sources	Nutrient Analog	Principal Biospheric Reservoirs	Degree of Food Chain Transport	Successive Trophic Level Concentration	Critical Organs (Vertebrates)	Assimilation
Light Metals (Group IIA) (continued)							
^{226}Ra (1600 years)	^{238}U Decay Series	Ca	Lithosphere	Moderate	<1.0	Bone	Moderate
Important Exposure Modes: Ingestion, Absorption, Uptake, External γ Retention (T_{biol}): High (years)							
Noble Gases							
^{37}Ar (35 days)	Activation	None	Atmosphere	Negligible	Negligible	Skin	Negligible
Important Exposure Modes: Submersion Retention (T_{biol}): Negligible							
^{85}Kr (11 years)	Fission	None	Atmosphere	Negligible	Negligible	Skin	Negligible
Important Exposure Modes: Submersion Retention (T_{biol}): Negligible							
^{133}Xe (5.3 days)	Fission	None	Atmosphere	Negligible	Negligible	Whole body	Negligible
Important Exposure Modes: Submersion Retention (T_{biol}): Negligible							
^{222}Rn (18 days)	^{226}U Decay series	None	Lithosphere, Atmosphere	Negligible	Negligible	Lung (from daughters)	Negligible
Important Exposure Modes: Inhalation of daughters Retention (T_{biol}): Negligible							
Heavy Metals							
^{51}Cr (28 days)	Activation	None	Soil, Sediment	Very low	< 10^{-2}	Lung, GI	Very low
Important Exposure Modes: Adsorption, Inhalation Retention (T_{biol}): Moderate-High (years)							
^{54}Mn (300 days)	Activation	Mn	Soil, Sediment	Mod.-High	<1.0	GI, Liver, Lung	Moderate
Important Exposure Modes: Ingestion, Inhalation, Adsorption, External γ Retention (T_{biol}): Moderate (days-weeks)							
^{55}Fe (2.6 years)	Activation	Fe	Soil, Sediment	Mod.-High	<1.0	Spleen, Lung	Moderate
Important Exposure Modes: Ingestion, Inhalation, Adsorption Retention (T_{biol}): Moderate-High (years)							
^{60}Co (5.2 years)	Activation	Co	Soil, Sediment	Mod.-High	<1.0—10 ²	GI, Total body, Lung	Moderate
Important Exposure Modes: Ingestion, Adsorption, Inhalation, External γ Retention (T_{biol}): Low (days)							
^{65}Zn (245 days)	Activation	Zn	Soil, Sediment	Mod.-High	<1.0	Total body, Liver, Lung	Moderate
Important Exposure Modes: Ingestion, Inhalation, Adsorption, External γ Retention (T_{biol}): Moderate-High (months-years)							

TABLE 11.4. Continued

[illegible]

TABLE 11.4. Continued

Radionuclide ($T_{1/2}$) ^a	Sources	Nutrient Analog	Principal Biospheric Reservoirs	Degree of Food Chain Transport	Successive Trophic Level Concentration	Critical Organs (Vertebrates)	Assimilation
Actinides (continued)							
²³⁸ U (4.5 x 10 ⁹ years)	Natural	S, Se?	Lithosphere	Low-Moderate	<1.0	GI, Kidney, Lung	Very low
Important Exposure Modes: Ingestion, Inhalation, Uptake, External γ							
Retention (T_{biol}): Moderate (months)							
²³⁹ Pu (2.4 x 10 ⁴ years)	Activation	None	Soil, Sediment	Very low	<10 ⁻²	Bone, Lung	Very low- Negligible
Important Exposure Modes: Ingestion, Inhalation, Adsorption							
Retention (T_{biol}): High (years)							

Source: Modified and reset from Whicker and Schultz 1982, pp. 163-166. Reprinted with permission from CRC Press, Inc., Boca Raton, Florida, copyright 1982.

There are, of course, considerable differences among members of a given group, and the categories therefore overlap. However, the broad outlines, based upon an enormous investment of time, effort, and resources, can be considered reasonably well established by virtue of this work.

B. Extensions and Generalizations from the Hanford Work

Near the end of the decade of the 1960s, the Hanford group produced a master plan for bioenvironmental work at PNL. The organization became the "Ecosystems Department," managed by Dr. Burton Vaughan.^(a) During a sixteen-year period, Dr. Vaughan and his colleagues in the Ecosystems Department were responsible for developing the biochemical and geochemical basis underlying many environmental contaminant phenomena. A new school of thought was developed around the concept of biological availability and the processes accounting for molecular speciation of contaminants. This work culminated in the E.O. Lawrence Award to Dr. Raymond E. Wildung for "particular contributions on plutonium biological availability through food chains and on nutrient availability in lake ecosystems (see chapter 15). This later period also saw the development of significant work on the role of radiation and heavy metal stressors in increasing disease in fish and shellfish. Particular mention should be made of work on immune suppression following low tritium radiation doses (see section VI F), work at the Marine Laboratory on metallothioneins induction and shellfish viruses, and work on the multiple etiology of columnaris disease (see section VI B).^(b,c) Facilities suitable for experimental work in both aquatic

(a) Richard Foster, who can be regarded as the father of the Hanford ecology programs, went to a post involving population radiation dose assessment, but his influence on aquatic biology never ceased. Herbert Parker was the grandfather of these programs.

(b) This and several other extensions, and updatings in this section, and in section VI were supplied by Dr. Vaughan as a result of his review of the manuscript. The author is grateful for these authoritative additions.

(c) In 1985, Dr. Vaughan became an assistant director of research at PNL, and the Ecosystems Department consolidated with both Geosciences and Atmospheric Sciences to form a large Earth Sciences Department with wide multidisciplinary capability.

and terrestrial biology were included in a new building constructed by AEC. This facility is pictured in figure 11.9A.

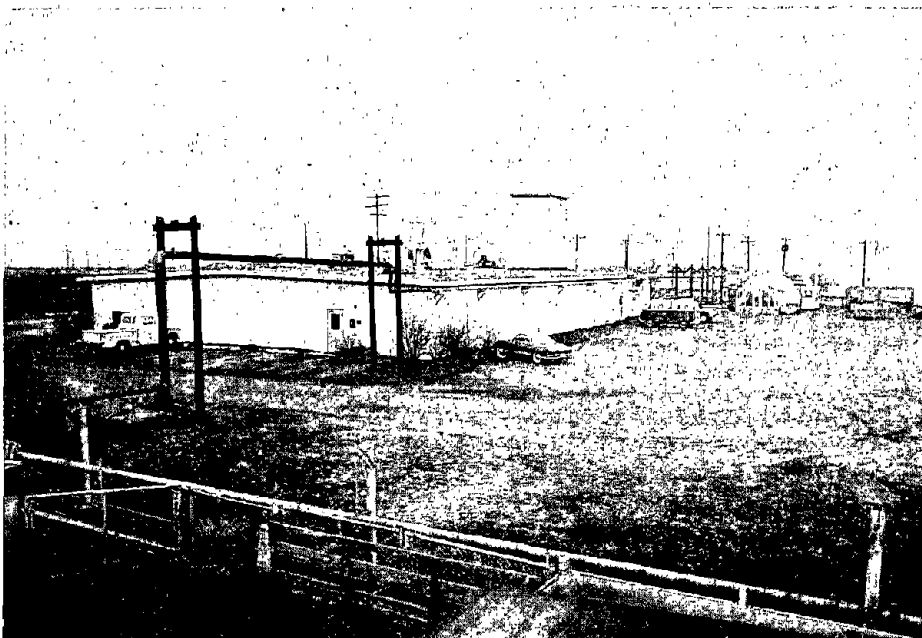


FIGURE 11.9A. Facilities for ecological research at Pacific Northwest Laboratory (Hanford) as they existed in 1964. (Courtesy of Pacific Northwest Laboratory.) The contrast to the original hutment (figure 11.1) is obvious.

Furthermore, the oceanographic and marine bioscience capabilities were consolidated and expanded with a laboratory at Sequim, Washington. Particular emphasis was placed on determining the bioavailability of contaminants, both radioactive and chemical. Research on the induction of metallothioneins in marine fish, isolation of these compounds, the range of their specificities, and the extent to which they protect from the toxic effects of heavy elements, all reached a high point of development at the laboratory at Sequim. This laboratory also pioneered in the development of methods for dealing with multiphase, complex mixtures such as petroleum, where fish, for example, may "see" a continuing shift in the "spectrum" of hydrocarbons they might be exposed to during a spill. A view of the new building at Sequim, built by Battelle, is shown as figure 11.9B.

We will be able to discuss only a few sets of generalizations from this work. Fortunately, the many symposia quoted in section IV provide ready access to aspects we cannot consider. A synthesis of PNL's environmental research on complex mixtures can be found in Fickeisen and Vaughan (1984).

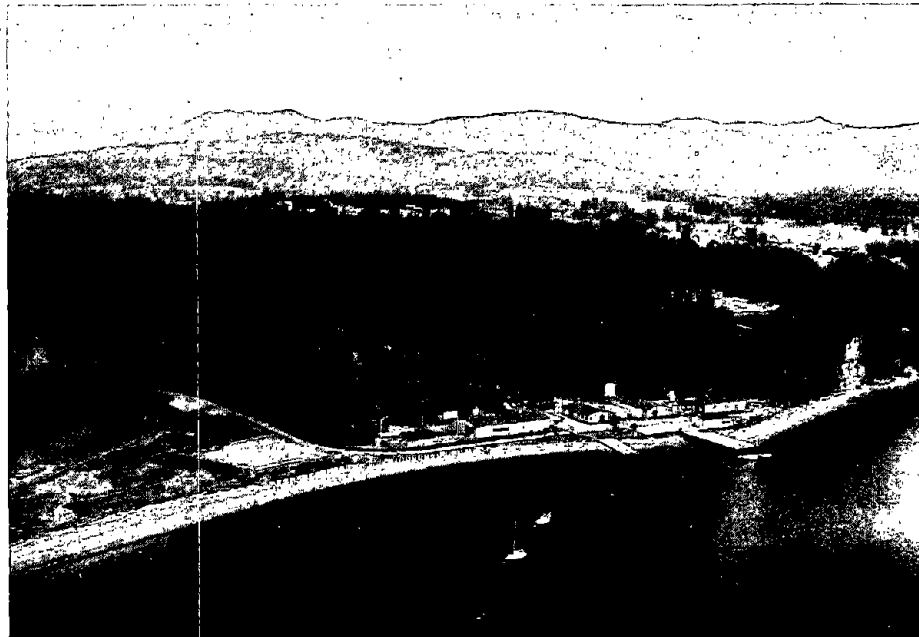


FIGURE 11.9B. Battelle, Pacific Northwest Laboratories' marine research facility at Sequim, Washington, on Puget Sound. (Courtesy of Pacific Northwest Laboratory.)

1. Generalizations from Columbia River Studies

The work extended not only the length of the Columbia River below the reactors but into its estuary and the north Pacific Ocean many miles from the mouth of the estuary. Among the firm conclusions are the following:

- a. Despite concentration factors that might appear quite high,^(a) even people who consumed extraordinary quantities of resident fish would have reached no more than one quarter of the population dosage limit recommended by the ICRP. Since the discharges have been declining steadily since 1970, there is little likelihood of this amount being exceeded in the future. These figures stand in considerable contrast to the story, for example, of the Animas River cited above, a situation reflecting neglect in the early years.
- b. The more prominent radionuclides found in the Columbia River effluent were ^{24}Na , ^{32}P , ^{51}Cr , ^{64}Ca , ^{65}Zn , ^{76}As , and ^{239}Np . Several of these have short half-lives and disappear rapidly. In the ocean environment off the mouth of the Columbia, the important nuclides are ^{51}Cr and ^{65}Zn . Since ^{51}Cr has a

(a) Concentration factors can be very deceiving, since the base line in many freshwater environments is very low and frequently variable. Also, there can be no true concentration factor stated unless the system is in equilibrium or a steady state.

short half-life and ^{65}Zn has a moderately long half-life and is quite mobile, it is the latter that has attracted the most attention. (As we will see in chapter 12, complementary work with ^{65}Zn was being done at the Pacific Proving Ground.)

- c. A large portion of the radioactivity entering the river is combined with the sediments, particularly bottom sediments. This was obvious very early. Recently, a sophisticated analysis using mass spectrometry was carried out by investigators from Oregon State University and the Savannah River Laboratory. Beasley et al. (1981) measured the ratios of ^{240}Pu to ^{242}Pu and of ^{240}Pu to ^{239}Pu in sediment cores raised during August 1977 from the McNary Reservoir downstream of the plant and the Ice Harbor Reservoir on the Snake River, a tributary of the Columbia that had no reactor-produced plutonium. They could thus distinguish between plutonium arising from worldwide fallout and that from the Hanford reactors. Two items were of special interest. The radioactivity of the sediments in the region around McNary Dam indicated that significant depositions of reactor plutonium had occurred in this first major impoundment below the reactors. While easily measurable amounts of all radionuclides did traverse the length of the river and enter the Pacific Ocean, the degree of deposition in relatively local areas must be reckoned with in any estimate of hazard. Also, it was estimated that about a quarter of the total plutonium inventory in sediments behind McNary Reservoir came from the Hanford reactors. The rest was from global fallout.
- d. The Hanford effluents "tagged" not only river currents but biota in all compartments of the system. The movement of the Columbia River plume along the Pacific coast to the north of the estuary in summer and to the south in winter was clearly established; also the behavior of the Columbia River plume in the open Pacific could be followed and its depth measured (it was surprisingly deep at times). All of these findings have a bearing on any attempts to establish critical population groups and critical pathways. Indeed, important basic information on the physics, chemistry, and biology of complex freshwater, estuarine, and marine ecosystems developed from these bonus tracer observations from a vast unplanned experiment.
- e. There is a notable absence of biological effects in these aquatic ecosystem studies. Despite diligent searching, no biological effects could be found from either the radioactive or chemical pollutants present.^(a) For example, Nelson from the University of Washington studied effects on larvae of the Pacific oyster, considered a critical organism in this system. He used ^{65}Zn , ^{51}Cr , and ^{90}Sr - ^{90}Y , as well as stable zinc and chromium. In laboratory investigations, the concentrations of these elements required to produce abnormal oyster larvae were over a million times those found in the breeding areas such as Willapa Bay (Nelson 1972). Small wonder that effects were not established in the ecosystem.

The search for effects was continued, however, using numerous ponds and streams on the Hanford site. A summary paper by Emery and McShane (1980) gives a cogent review of the work and its results; the abstract follows.

(a) It would be foolish to conclude that there were no effects of any kind due to the complexities of the system. However, the fact that none were found in such extensive work is significant.

Limnological and radiological parameters were investigated in ponds and streams on the Hanford Site to develop general radioecological profiles. All but one aquatic system receive low-level aqueous radioactive wastes from nuclear facilities. The remaining system is a pond formed by surfacing groundwater and contains radioactivity as a result of evaporative concentration of naturally occurring radionuclides. Attempts were made to determine whether the amounts of radioactivity present in each aquatic system could be related to ecological variation occurring among them. Maximum dose from the sediments and nuclide concentrations in the water were used to differentiate these systems radiographically. While Hanford ponds and streams could be grouped into three nuclide content categories, only one system (100-N Trench) had dose rates exceeding 1 R/week. However, maximum α concentrations in Z-19 Ditch water and maximum β - γ concentrations in 100-N Trench water both exceeded 10^4 pCi/l.

These aquatic environments support populations of commonly occurring algae, macrophytes, invertebrates and in some cases, fish. Although the algal populations contain less variety in 100-N Trench and Z-19 Ditch, variety in other types of biota are not apparently associated with amounts of radioactivity. Community structures in these systems appear to be as diverse as those in the Columbia River but less diverse than in some offsite streams. The productivity of plant life, invertebrates and fish in these systems does not appear to be associated with the relative difference of nuclear waste contamination. Furthermore, their rates of productivity resemble those measured in aquatic environments not associated with nuclear activities. Since these ponds and streams cannot be clearly differentiated from offsite systems or among themselves on the basis of a general ecological profile, this survey provides no conclusive evidence that the nuclear wastes discharged into Hanford ponds and streams have affected the colonization, diversity and activity of biota that appear in them.

A significant ecological feature in the Emery and McShane study was the incorporation into its sampling design of both seasonal biomass change and spatial distribution of biomass for all major trophic levels. At maximum, vector transport of plutonium by all biotic routes off U-pond,^(a) the most highly contaminated pond on the Hanford site, was trivial, and it was exceeded only by the investigators in the process of removing their samples!

These findings are reassuring. No horrible mistake seems to have been made. Indeed, it is easy to find ecologists who will state that the building of dams and the elaborate systems for irrigation have done much more to the ecology of the Columbia River than the Hanford effluents did or ever could have, even had they been less well controlled. We must express appreciation once again to those far-sighted individuals who stimulated the research programs on the river and its biology and insisted on the most rigorous of controls.

Nevertheless, contamination does exist.^(b) There is a substantial reservoir of radioactivity in the sediments all along the river. These must always be considered in planning any major activities that would disturb them or, in the event of unprecedented high water, that might sweep up sediments deposited many years before. Fortunately, the passage of time contributes to the gradual decay of the radioactivity of these deposits.

2. Terrestrial Work at Hanford in the Later Years

A considerable portion of the later work at Hanford in the field of terrestrial ecology extended investigations we have discussed earlier and in other

(a) The U-pond has since been decommissioned.

(b) Its justification is not an appropriate subject here (see, however, Alverson 1972, p. 856).

chapters. There was continued interest in the dispersion and effects of iodine, ruthenium, and, as we will review later, of the actinides. There was considerable work on the passage of radionuclides through arctic food chains, particularly as developed by J. J. Davis, and of fallout radionuclides in the local environs as well as at the test sites. There were laboratory investigations of the solubilization of radionuclides deposited in soil and their uptake by plants (chapters 13, 15). There was continued follow-up of the movement of radionuclides in animal and plant populations indigenous to the site.

In 1969, it was evident to the PNL Terrestrial Ecology Section that environmental radiation doses at the Hanford site were far too low in native plants and animals for any radiation effect to be expected. While monitoring radioelement movement in fish and wildlife food chains continued at the Hanford site, the research staff in terrestrial ecology took a different course from that at Oak Ridge and Nevada Test Site. The Arid Land Ecology Reserve, a forerunner of the National Environmental Research Park (NERP) system was established. This was the first Department of Energy (DOE) site dedicated as a Federal Research Natural Area. The 110-mi² reserve was dedicated to the study of wildlife, and vegetational and water dynamics typical of semiarid regions. By 1983, over two hundred university researchers had collaborated in these studies, and some sixty dissertation studies had been sponsored. Apart from wildlife studies, one of the main contributions of the NERP program was to show how evapotranspiration and other vegetational features could be modified to minimize entry into food chains of radionuclides buried in soil.

In the wildlife area, Dr. Lee Eberhardt and his colleagues contributed a distinguished series of statistical studies dealing with population estimation and spatio-temporal considerations in the design of biological monitoring programs.^(a)

Special note should be taken of the Ringold Farms study. It provides an excellent model for onsite evaluation work. It began in mid-1962, and the results were published in 1965 (Nelson and Foster 1965). Ringold Farms is a small farming area (about five hundred acres) on the Columbia River about thirteen miles downstream from the nearest production reactor. Columbia River water is used for irrigation. It is also about thirteen miles downwind from the separations plant. It is the closest area of active farming to both facilities.

There had been regular sampling of air, water, and farm produce from the area. These, along with measurements of external radiation levels, permitted a calculation of the probable range of dose to the inhabitants using many assumptions regarding dietary habits, etc. The availability in 1962 of a whole-body counting facility and the cooperativeness of the twenty people living in the Ringold Farms area provided an excellent opportunity to double-check the calculations and also to measure a group with presumably a higher-than-average chance of exposure. Zinc-65, ¹³⁷Cs, and ¹³¹I were particularly emphasized in the whole-body counts. As a check on isotopes like tritium, plutonium, uranium, etc. that would not show easily on the whole-body counters of the day, bioassay measurements were made on twenty-four-hour urine samples.

The whole-body counts indicated little difference in ¹³⁷Cs and ¹³¹I contents from those seen in others subjected to fallout radionuclides alone. Zinc-65 was also present in the subjects. All values were far below maximum permissible body burdens. The highest was iodine in the thyroid, which reached about 4% of the permissible level.

(a) This and the previous paragraph were supplied by Dr. Vaughan.

The bioassay measurements showed ^{32}P at levels of 1% to 5% of the NCRP maximum permissible body burdens (chapter 16) and no ^3H or ^{239}Pu . There was a small amount of uranium that came from the well water.

This study was necessarily small in number of subjects. However, it was consistent. The dietary habits of the subjects were known exhaustively. The usefulness of a whole-body counting survey for evaluation of environmental contamination was clearly established, and the correlation with doses estimated from intake values was reasonable.

A related set of studies involved the whole-body counting of thousands of school children in Richland, Washington, and the Tri-Cities area, as well as the use of portable counters for measurements of fishermen and extensive modeling for calculation of population dose. This was aimed first at checking out food-chain predictions (Foster 1979) and should be associated primarily with Dennis Harr, J. F. Honstead, and J. K. Soldat. (a) Battelle-Northwest reports and a paper at a Health Physics Society midyear topical symposium can be cited (Soldat and Honstead 1968; Soldat 1969; Honstead 1969 and 1970). The levels found were no cause for concern, and the information was primarily useful for checking intake routes. (b)

Later, the Hanford work developed into quite generalized modeling for estimating population doses from environmental contamination of many sorts (Soldat 1979). The original model had seventy-two parameters! Gradually, it was simplified by elimination of the less important factors, and it was computerized. The effect of many inherent parameters of the individual, such as age, was introduced, as were different routes of entry, different dose regimes (chronic versus acute), etc. An example of a typical report coming from this program is the one by Hoenes and Soldat prepared for the Nuclear Regulatory Commission (NRC) (Hoenes and Soldat 1977). This and other compilations from the group have been extremely useful to environmentalists, and they represent an important way in which operations and methodology generated for site-specific problems have been generalized for use in many situations (see section VI).

Finally, it should be noted that the Hanford group (now, of course, Pacific Northwest Laboratory, operated by Battelle Memorial Institute) got involved with the development of criteria for the decommissioning of sites no longer needed or used for nuclear activities (Soldat 1979). We will discuss this general activity in connection with Oak Ridge's later contributions.

- (a) Some of the original plans for environmental monitoring came from Jack Healy and Carl Gamertsfelder, who were in key positions in the earlier Hanford organization. Dennis Harr contributed considerably in the developing stages of the population exposure work (Soldat 1979), even though his name does not appear on the publications cited. The same applies to Karl Herde, whom we quoted in an earlier section.
- (b) An interesting sidelight on the early development of the bioassay techniques that preceded the wholesale application of whole-body counting has been provided by Karl Herde (1978). In 1947, Healy and the control group in the 200-West area (which included Herde) were having great difficulty establishing reliable techniques for bioassay of urine. They kept encountering high "background" counts, not only in the potentially exposed individuals, but in terrestrial and aquatic animals on the site and off, and in "controls." Since this was in the days before easy spectroscopy, they were doing gross counts and could not identify the isotope concerned. Suddenly, after an intensive search of the literature by Healy, it dawned on the group that the activity came from the body's natural content of ^{40}K !

C. Extensions at Oak Ridge

The environmental work in the later years at Oak Ridge was qualitatively much like what we discussed in section III. Quantitatively it boomed. In figure 11.10A, B, we see this transformation. Figure 11.10A pictures the "Ecology Program" of the Health Physics Division as it stood in summer 1955. In figure 11.10B, we see the "Ecological Sciences Division" standing before their new building in summer 1978. It is obvious that the Oak Ridge environmental program had become a strong force for all ecology.

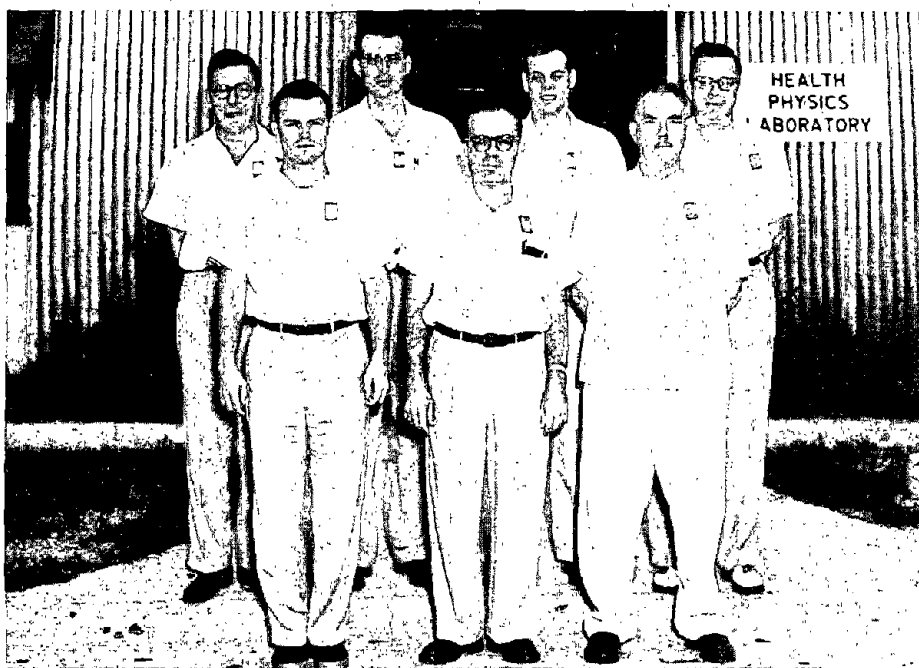


FIGURE 11.10A. Oak Ridge Ecology Program, summer 1955. (Courtesy of S. Auerbach.)

A measure of the contributions made is possible from a list of publications prepared in 1979 (ORNL 1979). This list is chronological from 1956 and reaches a grand total of 1,334 publications by the end of 1978, with an additional 11 indicated as "in press." Unfortunately, this is purely a chronological list. Anyone wishing to find papers on particular subjects is forced to dig.

1. Aquatic Programs

The Clinch River, as we saw in section III, presented some problems comparable to the Columbia, some that were rather different. Generalizations can be gleaned from a comprehensive report of the Clinch River study issued in 1967 (Struxness et al. 1967).^(a) Some of these are:

(a) By this time, and in subsequent work, the scene had actually moved out into the Tennessee River and went for many miles below the Clinch River per se. Thus, the study is more comprehensive than the title indicates.

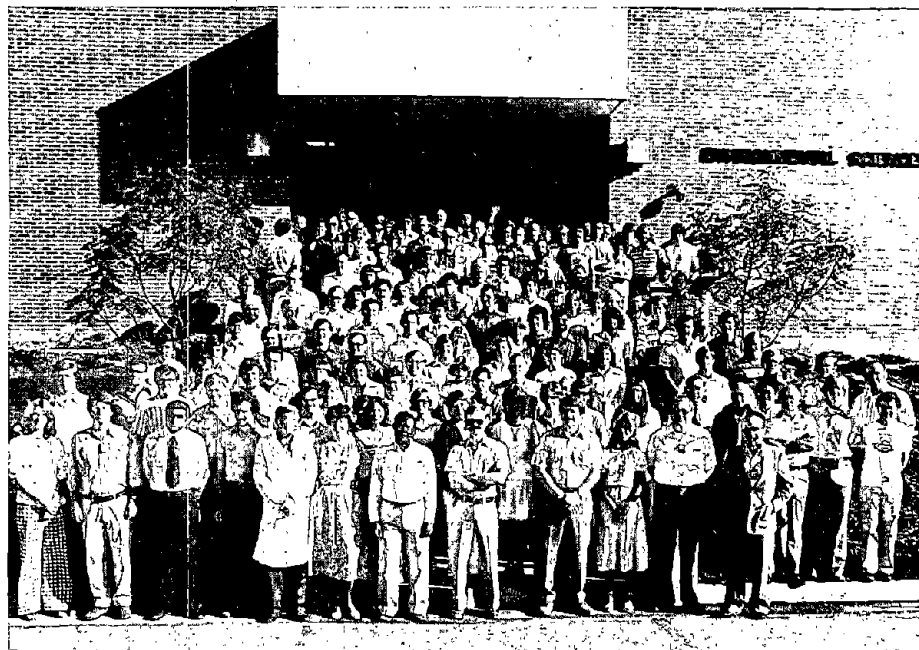


FIGURE 11.10B. Oak Ridge Ecological Sciences Division (now Environmental Sciences Division), summer 1978. (Courtesy of S Auerbach.)

- a. The river acted primarily as a tube for many radionuclides. Virtually all of the ^{90}Sr and ^{106}Ru entering the Clinch River passed through the river system in the water phase. It went as far down as Chattanooga, the last downstream station, 118 mi downstream from Oak Ridge, with relatively small changes except for radioactive decay.
- b. While these nuclides were in the water phase, they were not necessarily in solution. Much activity was attached to and was retained by very fine suspended particles in the river. (Note: These particles were not removed by high-speed centrifugation.)
- c. Most of the ^{137}Cs was associated with larger-sized suspended solids in White Oak Creek and Clinch River but was in solution or associated with very fine solids by the time it reached the Tennessee River.
- d. It was calculated that over 7,000 Ci of mixed fission products had been discharged into the river over a fifteen-year period.
- e. Of the above amount, about 200 Ci, or only about 1.5% of the total radioactivity released since 1944, could be accounted for in the bottom-sediments of the Clinch River. This stands in considerable contrast to the deposits in sediment of the McNary reservoir below Hanford. It reflects presumably the fact that no impoundment interposed. The information was based on analyses of core samples.
- f. There were some differences in the distribution of nuclides, with a definite loss of ^{137}Cs between the upper and lower reaches of the river, but not of the other primary radionuclides measured (^{60}Co , ^{89}Sr , and ^{106}Ru). There

- were: some differences in all of them between the more rapidly flowing upper reaches and the slower lower reaches of the river. There was very little deposited except along the sides of the stream in the former, deposition over the entire stream bed in the latter.
- g. All of these factors influence, of course, the details of the biological responses. Nevertheless, some generalizations regarding biological aspects can be made.
 - h. The white crappie was selected for study of uptakes in local fish, since fish-tagging showed that it did not migrate very far in the river.
 - i. River clams were found to be good indicator organisms for studying uptake and turnover of radionuclides and the extent of uptake at a given location. The clams are, of course, essentially immobile.
 - j. There was essentially no loss of ^{90}Sr from fish bones or clamshells, and the concentrations were directly proportional to the amounts in river water. By contrast, the retention half-time in flesh of the white crappie was on the order of one hour.
 - k. Effects were not seen in any of the biomass organisms studied, except for chromosome aberrations in *Chironomus* larvae. While these appeared, they seemed to be eliminated from the population by processes of natural selection and thus seemed not to represent permanent damage.
 - l. In the consideration of possible exposures, it appeared that ^{90}Sr and ^{137}Cs were the critical radionuclides and that drinking water and fish were the critical exposure pathways. Using these, total doses to teenage individuals (the critical age group) were calculated to be 3.2 and 0.45 rem from the Clinch and Tennessee Rivers, respectively.^(a) These figures are about one-tenth of the maximum permissible dose accepted at the time (Struxness et al., 1967, pp. 4-5).
 - m. For future projections, it was concluded that monitoring of the water and fish would be sufficient to keep track of what was going on in the river, with sampling of bottom sediments given a lower priority. Naturally, any unusual or extreme conditions would require reestablishment of the more detailed routines.
 - n. The Clinch River study actually involved six major technical and professional agencies, not just the Oak Ridge National Laboratory and the AEC. The authors of individual papers and the steering committee are convinced that such broad participation (and everyone contributed substantially) helped greatly to assure the success of the work. The agencies involved are listed as note 3 at the end of this chapter.

2. Terrestrial Programs at Oak Ridge in the Later Years

The substance of the Oak Ridge terrestrial ecology program was delineated in section III. Additional information was gathered in later years along the same lines as reviewed in the bibliographies and symposia already cited. (The most recent is by Klement and Schultz 1980.) New aspects included emergency planning for the Clinch Valley (Auxier and Chester 1973); several contributions to

(a) This difference may seem inconsistent with the earlier generalization that the isotopes went through the river system like a tube. We must remember that the water volume in the Tennessee River is considerably increased over the Clinch.

ecological considerations in siting power reactor plants (e.g., Auerbach 1970; Auerbach et al. 1971); Project Plowshare, which we will examine in chapter 14; and important ecological analyses of a variety of sites.

The calculation of dose to man from potential or actual environmental contamination gradually took on an identity of its own. Under the Health and Safety Research Division (new name for the Health Physics Division); a section called "Technology Assessments" grew under the capable direction of Paul S. Rohwer. The activity began as part of Project Plowshare (chapter 14). By the mid-to-late seventies, it had expanded to include over forty people and a broad program that included biotransport and dosimetry models, atmospheric transport research, alternative fuel cycle technologies, assessment of the radiological problems of mining and milling of uranium and thorium, development of environmental impact statements, radiological surveys of inactive sites or formerly utilized sites (see below), and a variety of special projects.^(a)

The radiological surveys of inactive and formerly utilized sites deserve special attention since they illustrate graphically the legacy that poorly controlled activities can leave.^(b) Figure 11.11 gives the geographical distribution of the more important of these survey sites as of 1978.

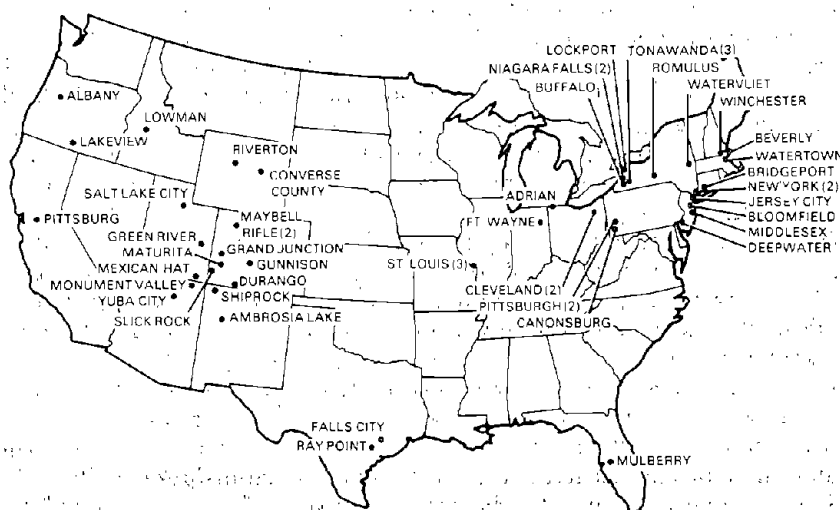


FIGURE 11.11. Geographical distribution of radiological survey sites (from ORNL 1979).

Some of these were uranium mills. However, many of those in populated areas represent old sites used during the MED days, even before, as well as, in

- (a) To a degree, the ORNL growth into assessment was parallel to that we have already mentioned at Hanford.
- (b) None of these are comparable in any degree to the notorious toxic waste dumps left by chemical industry operations (e.g., Love Canal on the Niagara Frontier), but they have the same implications qualitatively.

some cases, by the AEC in the 1950s. These had been turned back to the public domain for other uses. In the last days of AEC, i.e., 1974, a program was initiated to determine the condition of these sites. It was continued under AEC's successor agencies, ERDA and DOE. The results ranged from finding of only very localized contamination within some bunkers used for storage of pitchblende at the former Seneca Army Depot in Romulus, New York, to widespread and potentially serious contamination at sites such as the former VITRO Rare Metals plant at Canonsburg, Pennsylvania, and the former Horizons, Inc. Metal Handling Facility at Cleveland, Ohio (DOE 1977, 1978, 1979a,b; ORNL 1978).^(a) With over one hundred sites to look at, the personnel from the ORNL Health and Safety Research Division were busy throughout the country. Most of the sites were found to be within prescribed limits for exposure of the public. Some were from a little to considerably over the established limits. The worst problems occurred where the radium-containing portion of uranium ores had been discarded (see earlier discussion of uranium mills), particularly sites such as the one at Canonsburg, which had been used as early as 1911 to 1922 and 1930 to 1942 to extract radium from carnotite ore or scrap materials. Here there were significant amounts of ^{222}Rn in the buildings, of radon decay products on surfaces, and of ^{226}Ra both as a surface contaminant and in the ground beneath the buildings and around the site. The latter contributed significant gamma doses, while the airborne radon daughters in some of the buildings might go as high as 2 Working Levels (chapter 3).

All of this has led to many dilemmas regarding remedial action, particularly agreement on suitable criteria. The levels for recommending remedial action can be moved at least an order of magnitude by differences in assumptions regarding metabolic constants, e.g., the absorption from the gastrointestinal tract (more in chapter 16). Thus, the question of the relative availability of radionuclides that have passed through an environmental chain or just resided in the environment for long periods has become important enough to stimulate considerable research, at Oak Ridge, at Hanford, and at other places.

In conclusion, we can state with assurance that the radioecology work at Oak Ridge in the later postwar years has been qualitatively and quantitatively very significant. Perusal of the many literature reviews cited herein will provide further details.^(b) We will learn more of the research in chapters 13 and 15.

D. Work at Other Laboratories in the Later Years.

Since the discussions in the balance of this chapter and most of those in the subsequent chapters concerning the environment will not be organized laboratory by laboratory, this section is written for the convenience of the reader wishing to spot particular laboratories and their general orientation toward

(a) This author is indebted to Dr. Paul S. Rohwer, ORNL, for making copies of these reports available.

(b) The recent revelations and polemic regarding the release of large quantities of mercury at Oak Ridge (Marshall 1983) led to the conclusion that vigilance cannot be relaxed, and also to the conclusion that chemical waste problems in the United States are probably much more critical for the future than radioactive wastes, except for the nagging problem of spent reactor fuels.

radioecological work in the years from the midsixties on. The descriptions are mostly cryptic, since details appear throughout other discussions. These are, of course, in addition to PNL and ORNL, already described.

1. Brookhaven National Laboratory

The primary involvement of BNL with radionuclides in the environment was its continuing (twenty-five years) in-depth study of the inhabitants and environment of the Pacific Proving Ground. The work resided largely in the Medical Division until very recently. With increasing emphasis on dosimetric problems and retirement of some key medical people, the center of gravity has shifted to the Safety (Health Physics) Division. This work is discussed in chapter 12.

2. Health and Safety Laboratory, New York

The influence of this group on fallout measurements and implications will be apparent in chapter 12. Its role in the radon and uranium miner saga has already been told (chapter 3). Its influence on investigations of radiation problems around mill tailing sites was expanded during this period to consideration of the elevated radioactivity from uranium, radium, and radon around sites of phosphate rock mining and handling. Very recently, they have devoted attention to the questions raised by radon levels in buildings. As always, HASL has been especially contributory to the development, calibration, and operation of instrumentation and as a voice of experience in many of the projects.

3. Idaho Falls Laboratory

With its vast and remote areas, the Idaho Falls facility was an excellent site for field tests of a special nature that could not be easily accommodated at the NTS. These will be reviewed in chapter 14. It, too, has contributed much to methodology, especially radiochemical analysis procedures.

4. Los Alamos Scientific Laboratory

As in the earlier years, Los Alamos's primary orientation to environmental work was toward the tests (chapter 12). This included special interests in plutonium contamination (chapter 14). There was further work on liquid waste discharges and movement of plutonium and cesium in soils of the Los Alamos environs (Hakanson and Bostick 1976; Nyhan, Miera, and Peters 1976).

Because Los Alamos was among the earliest laboratories to have a whole-body counting facility, much work was done on identifying the body burden of fission products in the local and general population. Measurements in the Los Alamos population, begun in 1955, were continued for two decades.

In the 1973 annual report, we find an Environmental Studies Group was identified by name and a proposal made for a national environmental research park at Los Alamos. Radioecology studies of liquid waste disposal areas and of the Trinity bomb site (chapter 12) are mentioned. In 1974, we find description of the elaborate wind-tunnel apparatus used for determining resuspension of surface contaminants (chapters 14 and 15). In 1976, we find a fairly detailed account of ecological studies on uranium (Hanson and Miera 1977, 1978).

The uranium studies represent a classic onsite study. Over a thirty-three-year period, over 100,000 kg of natural and depleted uranium had been dispersed^(a) at one location on the Los Alamos grounds, E-F Site. Uranium concentrations in soil and biota indicated that only very small amounts of the material had moved "any appreciable distance" from the point of origin. An effects study concentrated on invertebrates, mostly ticks and mites living in the area. The areas of highest uranium activity (as high as 41% uranium in solution) showed significantly lower populations of these insects than control areas. Whether this represents a chemical or radiological effect is not discussed.

We will see more of Los Alamos work as we proceed.

5. Lawrence Livermore Laboratory

In addition to its large involvement with the NTS and Pacific Proving Ground, the Lawrence Livermore Laboratory did various site-oriented studies. For example, they looked at the interactions between radionuclides in the discharge canal of the Humboldt Bay Power Plant near Eureka, California, and oysters in the canal. They found behavior indicating binding to particles in the sediment and an important role of these in the accumulation of some, but not all, of the nuclides in the oysters (Harrison, Wong, and Heft 1976a,b). They calculated the radiological dose to man through the marine pathway at this same reactor (Noshkin, Robison, and Harrison 1976). Besides their large involvement with plutonium and the actinides in the environment of the test sites, they considered global problems and some specifics such as ^{238}Pu from the testing of SNAP devices (Systems for Nuclear Auxiliary Power) in the waters near San Clemente Island, California (Noshkin et al. 1981). Details in later chapters.

6. New York University

The New York University (NYU) study of the Hudson River estuary is one of the longer-standing, more comprehensive surveys of a power reactor site. It began in 1964 and is continuing. It extends from the mouth of the Hudson River to a considerable distance upstream from the Indian Point Reactor, which is about forty-two miles north of New York City. The average flushing time of the estuary is about thirty days, slow in comparison with the Columbia and Clinch Rivers, except for the impoundments, but rapid in comparison with many lakes.^(b) The principal nuclides released range from 725 Ci of tritium to less than 0.01 Ci of ^{90}Sr per year (in 1971). The most important ones are ^{137}Cs , ^{134}Cs , and ^{54}Mn . The tritium, while initially present in large quantity, is rapidly exchanged and of much lower toxicity (see section VI).

The development of the NYU work can be followed in annual reports and occasional published progress reports (Lentsch et al. 1970; Wrenn et al. 1974). The easiest source is a pair of review papers given at a conference on radionuclides in the aquatic environment held at the University of Rochester (Jinks and Wrenn 1976; Wrenn and Jinks 1976). The first describes primarily the transport of radiocesium and modeling of same. The second is a broad review of the

(a) This was not dumping, but the result of a "dynamic testing program" with high explosives.

(b) Mean retention time in Lake Superior is, for example, 189 yr; in many smaller lakes, it is on the order of months to years.

work on the Hudson River estuary and dosimetric implications from it and many other aquatic environments in the United States into which nuclear fuel cycle effluents have been deposited (e.g. Colorado River, Animas River, Lake Michigan and other Great Lakes, Mississippi and Missouri Rivers).

The estuarine environment is especially interesting as the NYU people found, because the water varies in salinity. In periods of rapid river flow, the water near the Indian Point Reactor may be nearly fresh. In periods of low river flow, the tidal exchange brings salt water much further inland, and the water near the reactor may contain enough additional cations to influence greatly the combination of radionuclides with suspended particles. Jinks and Wrenn showed that the percentage of ^{137}Cs and ^{134}Cs in the dissolved state at Indian Point varied from less than 20% when the water was fresh to over 90% when chloride concentrations exceeded 2 g/l. (The balance was attached to particles.) The relationship was logarithmic, and distribution coefficients could be calculated.^(a) There was also a considerable difference in the rate of desorption of cesium from bottom sediments at different times of year. The maxima were in the warmer months and represented again the change in distribution coefficient with concentration of ambient cations. These phenomena are, of course, reflected in the concentrations of radionuclides in the biota and in the calculated doses to humans. The dose is not at all a constant value, even if other variables remain constant. These phenomena, of course, pertain to all estuaries, not just the Hudson River, but the variations in salinity may be greater in it than in some others. Nevertheless, mean or maximum values can be used and potential hazard estimated.

The time course of the mean concentration of ^{137}Cs in sediment water and biota over a ten-year period is given in figure 11.12, taken from the review by Wrenn and Jinks.

Note that the minimum activity in the water corresponds with the end of the major fallout contributions, and that, like the other river systems described, the radioactivity of the bottom sediments rose steadily throughout the period. Although fish and aquatic plants had about the same content, the fish were the major route to man. Assuming consumption of 30 g of the fish per day, the calculated whole-body dose to man from all of the reactor nuclides in the Hudson River was 0.19 mrem/yr for 1971-1972 (Wrenn et al. 1974). Being on the shoreline at the nearest beach for 200 hr/yr would contribute 0.06 mrem/yr and swimming for the same period at the same place about 0.01 mrem/yr. These can be compared to allowable annual doses to the surrounding population of 3 mrem to the whole body or 10 mrem to any individual organ (Code of U.S. Federal Regulations, 10 CFR Part 50, Appendix I, September 1975).

The Wrenn-Jinks analysis proceeds to other reactors, both boiling-water and pressurized-water types, and other bodies of water. It concludes that radio-cesium will be the critical radionuclide in all fresh waters, except if a drinking water intake is near the source of the contamination. In this event, ^{131}I may be the critical nuclide. We see again in the NYU work that an analysis begun around a single site can evolve into general population dose considerations.

Incidentally, Wrenn and Jinks point out that in many systems, such as mining and milling, ^{226}Ra can be the critical radionuclide and should not be forgotten

(a) Another way of expressing the phenomenon is by relating the biological accumulation coefficient to the concentration of potassium. Jinks and Wrenn (1976) do this for several aquatic systems.

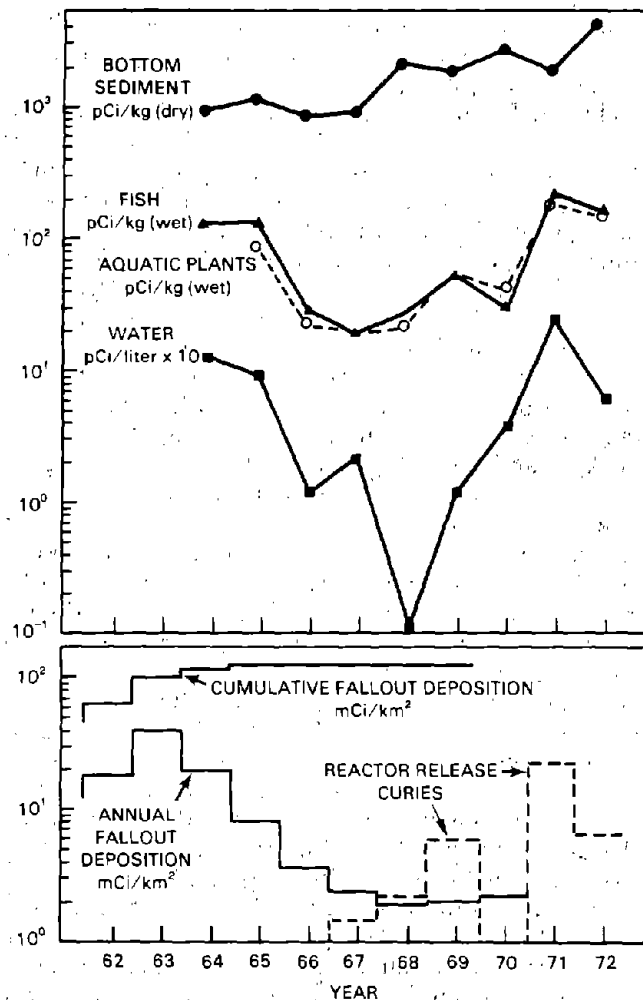


FIGURE 11.12. Cesium-137 content of sediment water and biota in the Hudson River: averages of 1962–72 along with fallout and reactor inputs. The increase in reactor releases (March 1971–March 1972) was due to leakage between primary and secondary cooling systems. These have remained at a constant lower level since upgrading of the radwaste system. (Redrawn from Wrenn and Jinks 1976. Reprinted with permission of Butterworth Publishers, Stoneham, Massachusetts, copyright 1976.)

in our zeal to measure fission products and activation products in connection with the nuclear fuel cycle. We have seen ample evidence of this fact already.

7. Rocky Flats Plant

A large plutonium fabrication facility was built by the AEC in the 1950s and was operated by the Dow Chemical Company at a site near Golden, Colorado, in Jefferson County, not far from Denver and Boulder. There were small routine

releases of plutonium from the plant stacks from start-up in 1954 because the filter system was not and could not be absolute. (Some very small particle sizes could get by.) The extremely pyrophoric nature of plutonium under conditions suitable for machining led to occasional fires despite elaborate precautions. There were major fires at the plant in 1957 and in 1969 that destroyed the integrity of the filter system and released significant quantities of plutonium to the environment. Measurements of plutonium in the soil and in water were carried out by local staff initially, then concerned groups from surrounding university and governmental laboratories began looking for plutonium. Edward Martell at the National Center for Atmospheric Research near Boulder, who had already had considerable contact with research involving radioactive materials, demonstrated the presence of plutonium in soil around the plant. He appears to have been an important force in the development of a subcommittee on Rocky Flats under the Colorado Committee for Environmental Information (1970). Also, a report was prepared (as a memorandum to the files) by the ESSA Research Laboratories (Dickson and Start 1970). The environs of the Denver metropolitan area were much closer to the plant by 1970 than when the site was selected and the plant built. Between that and the reputation for toxicity attributed to plutonium, the contamination around Rocky Flats became a cause célèbre.

As a result of all this, the experts from the Health and Safety Laboratory in New York were called in, and many measurements were made, particularly of soil samples and soil cores. There was clearly plutonium about, and, on the basis of isotopic ratio measurements, Rocky Flats plutonium could be identified (Krey and Hardy 1970). However, it turned out that the highest concentrations were not downwind of either the 1969 or the 1957 fire. They lined up squarely with leaking barrels of cutting oil laden with plutonium and stored out-of-doors (Krey and Hardy 1970). The concentrations were not an immediate danger to health, but were uncomfortably close to or even above the new standards then being set by the Environmental Protection Agency (EPA). It was decided on a somewhat ad hoc basis that inhalation was the primary hazard.

At a symposium on environmental plutonium held at Los Alamos in 1971, Hammond from the Rocky Flats plant presented data on the routine releases and the total amounts of plutonium from the uncontrolled releases. He also told the story of the cutting oil drum storage and the genesis of what gradually became something of a controversy between Martell and his measurements and measurements by the plant and by HASL (Hammond 1971). In 1972, the Martell group made their procedures and findings generally available in a publication (Poet and Martell 1972). They looked at surface waters and sediments as well as soil. Soon Krey published revised figures (Krey 1974), and Poet and Martell responded (Poet and Martell 1974). However, the differences were mostly matters of details of the origin of and depth of penetration of the plutonium, etc.

A total inventory and further details were made available by HASL in 1976 (Krey 1976). The integrated figures showed 3.4 ± 0.9 Ci of $^{239-240}\text{Pu}$ were deposited from Rocky Flats on public and private land.

There was a rash of interest in the particle size distributions in the soil because the chance of redistribution by wind was much greater for smaller than for larger particle sizes. Much of this work was done by Dow Chemical Company in-house.

The HASL and related reports indicated that the plutonium had probably penetrated deeper into the soil around Rocky Flats than at the NTS (chapter 14), e.g., as far as 13 cm with sizeable amounts below 5 cm. This led to gradual

interest in possible percolation into water supplies and into the ponds around the plant. Figures for plutonium content of water appeared in the draft environmental impact reports for the Rocky Flats plant site developed for the Colorado State Health Department in 1973 and for ERDA in 1977. The concentrations in water were below current federal standards, but they were not below standards being proposed at the time to account for changes in the valence state and thus solubility of plutonium when water is chlorinated for drinking purposes (Larsen and Oldham 1978).^(a)

The people from Hanford decided to investigate the behavior of plutonium in several ponds and two creeks near the Rocky Flats plant (Paine 1980), with particular emphasis on its possible export from the site to water supplies.^(b) As in the other studies, sediments were the major site for plutonium deposition, and it tended to stay there. Fish flesh and bone showed no levels above the minimum detectable. Some varieties of plankton discriminated against plutonium, but other biotic components, such as the phytoplankton mixture known as seston (Paine 1980), showed high concentration ratios. This work concluded that there is no direct evidence that concentrations of plutonium observed will result in a biological hazard to humans through the ingestion route; but that studies should continue.

Despite this relatively negative conclusion, C. J. Johnson of the Jefferson County (Colorado) Health Department^(c) mounted an epidemiologic evaluation of the population. He designated groups enclosed by different isopleths of plutonium concentration, viz., 50 to 0.8 mCi/km², 0.8 to 0.2 mCi/km², 0.2 to 0.1 mCi/km², and a control population outside of the lowest isopleth. Populations were over 150,000 in each area. In a preliminary report delivered at the Sixth International Congress of Radiation Research (Johnson 1979), he concluded that there were significant increases in age-corrected leukemia death rates in the more contaminated areas and an age-corrected, age-specific increase in death rate from lung cancer. He also reported an increase in the rate of incidence of testicular cancer. Other entities, such as bone cancer, showed no significant difference, while the rate for congenital malformations was said to be marginally higher.

Some of these results, like the increase in leukemia incidence, are not characteristic of the effects of plutonium seen in animals. Like many epidemiologic studies covering a relatively short period, and source terms that are subject to many uncertainties (as freely admitted by the authors), these conclusions have been questioned. Some of the staff at the Lovelace Inhalation Toxicology Research Institute (see chapters 9 and 10), viz., R. G. Cuddihy, W. C. Griffith,

(a) At about this time, and partly because of the Rocky Flats events, there were several proposals for fairly drastic reduction of the standards for population exposures to plutonium and the transuranic elements. Myers (1972) concentrated on the deposition of the insoluble oxides in pulmonary lymph nodes and suggested, as have others (see chapters 9 and 16), that they should be the "critical organ" rather than lung. By a quite different approach, Morgan (1975) aimed at a similarly lower figure. They were 67 and 170 pCi versus the occupational standard of 0.04 μ Ci and a population standard of 1/10, 1/30, or 1/100 of this.

(b) This was like the work around the Hanford ponds already reported and can be considered a parallel comparative study. See Emery, Klopfer, and McShane (1980) and Emery and Klopfer (1976).

(c) The Colorado Regional Cancer Center, the Division of Vital Statistics of the Colorado Department of Health, and others contributed.

and R. O. McClellan, prepared a formal review as an "in-house" DOE document (Cuddihy, Griffith, and McClellan 1979). P. W. Krey at HASL introduced some new information that would modify the contours fairly sharply in some instances (Krey 1979). For these methodological reasons and because of the unusual pattern of cancer distribution noted, the reviewers believe that there may be some artifacts in the analysis. Also, they point out that fallout radioactivity contributes much more to the total radiation doses in the Denver area than does plutonium from Rocky Flats. Thus, the operation can be regarded as in the category of "picking fly-specks out of pepper."^(a)

Recently, a group of epidemiologists at Harvard, at a private concern in Chestnut Hill, Massachusetts, and at New York University (Dreyer et al. 1982) concluded that the total dose from transuranic contamination of the area around Rocky Flats is so far below natural radiation background and that from global fallout that the "statistical power" of an epidemiologic study would not be sufficient to support such an effort. Others have concluded that the data warrant concern even though they require confirmation and advise a reanalysis by better methods and over much longer time periods.

No information has come to light on whether or not any further epidemiology work is being attempted. The Rocky Flats story will undoubtedly continue into the future. Whatever the final answer, there seems little doubt that the plant has been made more environmentally safe. We can be sure it will be watched with a baleful eye by the local population.^(b)

8. Savannah River Plant

The work at Savannah River in the later postwar decades included the movement of tritium in the estuary of the river, plutonium behavior in the environment, and a continuation of the type of work described in section III. A few reports will come up in the specific topic section to follow. The reader is referred to the many reviews already cited for additional work.

VI. Special Topics

Before we can proceed to other aspects of environmental research concerning radionuclides, we must pause for a brief summary of some special subjects that have important niches. Some of them are closely related to work around the production sites. Others are quite general. Thus, this section fulfills the survey functions of this chapter as much as its orientation to the production sites.

A. Marine Radioecology

It is obvious from the materials we have already reviewed, and will be even more obvious as we proceed through these chapters on environmental aspects of radionuclide research, that the twin problems of fallout from weapons tests and potential or actual disposal of radioactive wastes have required major research efforts on marine systems. These have become sufficiently organized and idiosyncratic to justify the designation of "marine radioecology."^(c)

(a) This terminology is that of this author, not that of the reviewers.

(b) It is reported that Dow Chemical decided to bow out as contractor because of the continuing problems of public relations.

(c) The IAEA organized many symposia embracing aquatic environments (IAEA 1960, 1963, 1966a,b, 1968, 1969, 1971, 1975, 1976a,b, and 1979a,b).

No doubt the field began with the work at the University of Washington Applied Fisheries Laboratory. Perhaps the first time the field received an identity of its own was with the 1957 report of the U.S. NAS-NRC entitled, *The Effects of Atomic Radiation on Oceanography and Fisheries* (1957). Clearly, marine radioecology has a much larger component concerning the kinetics of transport of substances in the sea and perhaps less conventional ecology than other varieties of marine ecology. In the early reports, it was clear that the presence of new, manmade radioactive materials in the sea allowed a gigantic tracer chemistry experiment with implications to the fundamentals of the transport processes in the sea. In fact, Craig (1957) suggested that isotopic tracer techniques could characterize physical processes in the sea and atmosphere; and Folsom and Vine (1957) suggested that water masses could be tagged by addition of fairly substantial quantities of radionuclides (Operation "Hare and Hound," for example). Obviously, the same can apply to large-scale biological experiments (Revelle and Schaefer 1957; Schaefer 1957).

It must be remembered, of course, that the sea already has enormous quantities of natural radionuclides such as ^{40}K , ^{14}C , ^{87}Rb , and uranium and thorium isotopes. Even the apparently large quantities added by humans are very small by comparison. They will not alter the physical and chemical properties of seawater, except locally. Indeed, were it not for concentration in organisms by adsorption (as of polonium on the giant kelp described in chapter 4) and by metabolic processes, the dilution factors would make the additions inconsequential.

What of the much discussed concentration possesses?(a) A tabulation of historical interest taken from a paper by Krumholz at the University of Louisville, Goldberg at Scripps Institution of Oceanography, and Boroughs at the University of Hawaii is given as table 11.5.

It is clear that the concentration factor varies greatly among chemical species, among organisms, and between soft and skeletal-type tissues. Much of marine radioecology has involved further elucidation of these factors, the reasons for the differences, and how they can be used to estimate radiation dose. The book by Polikarpov (1966) from the USSR devotes considerable space to these matters, including detailed analysis of the behavior of major groups of elements and specific elements of interest. The Stockholm symposium on radioecological concentration processes goes into still more detail to the tune of over one thousand pages (Åberg and Hungate 1967).(b)

A few generalizations can be made regarding marine radioecology that are worth keeping in mind for subsequent chapters. These are in addition to those made in section V A and apply only to the marine environment.

1. Organisms at the first trophic level (e.g., simple organisms) take up radionuclides primarily in the ionized state or by adsorption on body surfaces. Usually the elements most concerned are those with counterparts in the nutritional scheme.

(a) If the amount in the biological material is less than the amount in the medium, this same ratio gets called a discrimination factor. There are fewer of these in the marine than in the terrestrial environment. (See earlier caution regarding derivation and use of these factors.)

(b) Much can be learned by simple perusal of this volume. The research involves some very general and some very specialized environments (terrestrial, freshwater, and marine) and it is all concerned with transport of materials, primarily radionuclides.

TABLE 11.5. Approximate Concentration Factors of Different Elements in Members of the Marine Biosphere. The concentration factors are based on a live weight basis.

Element	Form in Seawater	Concentration in Seawater (micrograms/l.)	Algae (Non-cal-careous)	Concentration Factors			
				Invertebrates		Vertebrates	
				Soft	Skeletal	Soft	Skeletal
Na	Ionic	10 ⁷	1	0.5	0	0.07	1
K	Ionic	380,000	25	10	0	5	20
Cs	Ionic	0.5	1	10	—	10	—
Ca	Ionic	400,000	10	10	1,000	1	200
Sr	Ionic	7,000	20	10	1,000	1	200
Zn	Ionic	10	100	5,000	1,000	1,000	30,000
Cu	Ionic	3	100	5,000	5,000	1,000	1,000
Fe	Particulate	10	20,000	10,000	100,000	1,000	5,000
Ni	Ionic	2	500	200	200	100	—
Mo	Ionic-Particulate	10	10	100	—	20	—
V	?	1	1,000	100	—	20	—
Ti	?	1	1,000	1,000	—	40	—
Cr	?	0.05	300	—	—	—	—
P	Ionic	70	10,000	10,000	10,000	40,000	2,000,000
S	Ionic	900,000	10	5	1	2	—
I	Ionic	50	10,000	100	50	10	—

Modified slightly from Krumholz, Goldberg, and Boroughs 1957.

- Organisms at the second trophic level (e.g., zooplankton) tend to concentrate radionuclides that are in particulate form.
- There are large species differences and even large differences between individuals of the same species. These are largely unexplained.
- Uptake is, in general, more rapid and in larger amount in growing organisms and populations.
- There is no simple rule that can be generally applied regarding the transfer of radioactivity up the trophic structure. It all depends on who feeds on what.
- Retention is essentially indefinite in the calcified portions of organisms in the sea but may be very short in soft tissues.
- Many radionuclides partition into soluble and insoluble fractions.
- The chemistry of seawater is complex. While the buffering capacity is much greater than in freshwater systems, and this lends some stability to entities such as dissociation constants of compounds, there is no substitute for measurements instead of calculations. For example, Feldman (1976), at the University of Rochester, pointed out that equilibrium calculations are probably not valid for submicroconcentrations of radionuclides in seawater. He predicted and showed examples of the existence of radiocolloids in seawater. This may help explain some apparent anomalies.
- Despite what appear to be large concentration factors in organisms, the bulk of the radioactivity in seawater is in the nonliving phases. However, continual turnover by organisms and rapid repopulation can accomplish considerable transfer from water to biomass to deep layers of the ocean or the sea floor. Polikarpov (1966) shows how plankton organisms with a

concentration factor of 1,000 can accomplish transfer of radioactivity downward at ten times the rate of hydrological transfer. This was with a mixing coefficient of 0.1.

10. As in the freshwater systems already discussed, a significant portion of the activity in marine systems finds its way eventually to the bottom sediments.
11. As a crude generalization, it can be said that cesium, strontium, and zinc tend to exist in ionic forms in the sea, while ruthenium, cerium, zirconium, yttrium, niobium, and iron tend more to exist as colloids or suspended particles (Whicker and Schultz 1982).
12. Chemically analogous elements such as potassium and calcium in seawater may act as carriers for elements such as cesium and strontium.
13. The activation products and those fission products that tend toward colloid formation are, in general, of more biomedical concern than elements like strontium and cesium, in contrast to the terrestrial environment.
14. Marine systems handle the same spectrum of radionuclides quite differently from freshwater and terrestrial systems. A first contrast is due partly to the presence of much larger quantities of potential analogues in seawater. A second contrast resides partly in the much greater mixing in the aqueous as compared to the terrestrial environment.

The dramatis personae in all of this have already been named in part. We will meet others as we progress.

B. Effects of Radionuclides on Ecosystems

The first approaches to determining biological effects of ionizing radiation in ecosystems were directed toward individual organisms. As described in section II, the pioneering work was done at the University of Washington Applied Fisheries Laboratory during World War II. It began with x-irradiation of salmon and trout at various stages of development and gradually expanded to other aquatic organisms.

Donaldson and Foster (1957)^(a) give a succinct review. Algae and protozoa required extremely high doses (many thousands of roentgen units) to show lethal effects. Mollusks and crustaceans were somewhat more sensitive, requiring doses of a few thousand roentgens for 50% lethality. Fish were the most sensitive with an LD₅₀ on the order of 1,000 roentgens. *All* of these are higher than the LD₅₀ doses for higher vertebrates, including that calculated for humans.

Donaldson and Foster review also the radiosensitivity of different life stages of various aquatic organisms and report the usual greater sensitivity of gametes, eggs, and other rapidly developing stages. Qualitatively the effects were like those seen in "higher" organisms, although the time course was generally longer, presumably because of the lower temperatures. Genetic effects were seen also, but it appeared that the genetic apparatus of many of the aquatic organisms studied was relatively radioresistant compared to the cells of terrestrial vertebrates.

Immediately post-World War II, several field experiments were set up using large radiation sources. These were studies of terrestrial organisms. They have already been described briefly (Brookhaven; Oak Ridge; Dawsonville, Georgia,

(a) Details appeared in the University of Washington Applied Fisheries Laboratory reports cited by Hines (1962).

i.e., Emory University; Puerto Rico). All of them involved large radiation sources with rapid diminution of the intensity with distance from the source. They were primarily useful for determining relative sensitivity of trees and plants. Animal populations were too mobile, and their dose could not be determined. A special radiation field was set up at the NTS by N. R. French and associates from UCLA (French 1964, 1965, 1969, and undated) to provide both a relatively low-level chronic irradiation pattern and a tight enclosure to prevent immigration and emigration of the animal population (lizards and small rodents).

There were some surprises from these large field studies, e.g., the unexpectedly high radiosensitivity of the conifers. Since this work was all with external radiation sources, space prohibits further exposition here.

By contrast, effects work concerning radionuclides in ecosystems, either terrestrial or aquatic, has not produced as much information, nor could it be expected to. This is largely because massive contamination would be needed to produce doses comparable to those delivered by the large sources of gamma rays and neutrons. Instead, the search for effects from radioisotopes in natural ecosystems has had to rely on the doses delivered by whatever contaminating events have taken place. Even though the total amounts of radionuclides from fallout and other sources may have been large, the dilution factors have been very large also. Thus, the doses are not high except locally (chapter 12). Partly because of this difference in magnitude of the dose, and partly because of the tremendous resiliency of the ecosystems at low to moderate levels of perturbation, few clear bioeffects have been seen from radionuclide contamination except around highly contaminated local foci.^(a) The effects (or lack of effects) of radiation from radioactive wastes seen in the organisms of the dry bed of White Oak Lake at Oak Ridge, in the Clinch River, the Columbia River and its estuary, and the Animas River have already been described briefly. Effects of plutonium and tritium have been studied at the NTS. They have been minimal, as we will see in chapters 12 and 14.

Nevertheless, the story was not a monotonous litany of negative findings. Polikarpov (1966) ran through most of the literature from the USSR, eastern and western Europe, and North America on the effects of single and chronic doses of external radiation on a variety of aquatic organisms. This includes work with ova, larvae, etc., and is nicely summarized in the useful tables in his important book. For the chronic doses, he included effects of ^{89}Sr , ^{90}Sr , and ^{90}Y , mixed fission products in rainwater, etc. He looked at populations of periphyton to determine which forms dominated as a function of time and dose. On the basis of preliminary data, he predicted that incorporated radionuclides would be more effective on forms such as larvae or fry than a comparable dose from an external radiation source.^(b) He concluded that, despite problems with incomplete experiments and of extrapolating from laboratory to ecosystem, *no further radioactive contamination of seawater is admissible*, at least until marine radioecology has a chance to check out phenomena such as those he describes. Unfortunately, this author can find little evidence of a careful and formal

(a) We are discussing ecosystems or major components thereof, not the occasional effect of a high dose on individuals as at Enewetak.

(b) Polikarpov quotes work showing abnormalities in the larvae of the sea fishes at concentrations of ^{90}Sr , ^{90}Y as low as 10^{-10} to 10^{-12} Ci/l (10^{-5} to 10^{-6} pCi/l), and notes that these levels had already been reached at the Pacific Proving Grounds and in the Irish Sea.

follow-up of these findings in subsequent years in the same or in other systems. The observations seem to stand more or less alone.

The most difficult problem is, of course, the complex ecosystem itself. In interviewing many of the outstanding figures in radioecology for this book, the author has asked if they knew of or had any reason to suspect that there might be some exquisitely sensitive organism or process in some major ecological system whose disabling would have far-reaching effects (Donaldson 1979; Foster 1979; Seymour 1979; Auerbach 1979; Larson, Welander, and Bonham 1979; and others). They all answered in the negative. The ecosystem is too resilient for that. However, there are ways in which a subtle change could become a significant one.

In this connection, the book by Whicker and Schultz contains some revealing paragraphs. For example:

... An ultimate objective of radiation ecologists was to investigate the effects of ionizing radiation at higher levels of integration, efforts were made to irradiate populations, communities, and ecosystems in place.

The complexities associated with such investigations are formidable. A considerably greater degree of complexity is involved when one considers the effects of ionizing radiation (or any other stress) at the population or community levels as compared to the organism level, particularly when investigations are conducted in the field. At the community level, direct effects of radiation on individuals become intertwined with indirect effects of multiple interactions and secondary effects. In a natural community, niche space is available to populations only under the condition that their existence within a certain space and at a certain density is compatible with conditions imposed by the abiotic environment and by other members of the living community. Regulation of a plant or animal population is achieved by relationships of space, nutrient supply, available sunlight, water, and a host of other factors, all of which are affected by other populations of the biotic community. The result then is that changes observed in a community following irradiation are caused not only by ionizing radiation per se, but also by interactions and secondary effects which result from the inherent nature of that community and its supportive elements. Without ancillary information, the relative importance of factors responsible for observed changes in an irradiated community may be obscure. These complexities and resulting high costs of experimentation have restricted the number and magnitude of field investigations. (Whicker and Schultz 1982, Vol. 2, p. 119)

These questions were examined in some detail by John Strand, Dale Becker, and Paul Fujihara at Pacific Northwest Laboratory, and their deliberations resulted in a brilliant monographic publication in 1978, on columnaris disease in Columbia River fish (Becker and Fujihara 1978). The publication was, in fact, only the second monograph published by the American Fisheries Society in its 115-yr history. By the end of the 1950s, the Columbia River adjacent to the Hanford site had been considered the source of induction of high-virulence strains of the bacterial pathogen, *Flexobacter columnaris* and the source of their widespread dissemination among resident salmon species. Reactor-warmed water, as an enhancing agent for many bacterial diseases in fish, and radiation, as a potential mutagen, were seen as a complex of factors that might explain the rather catastrophic outbreaks of this disease. In this monographic study, various environmental influences on epizootic outbreaks were evaluated systematically, including temperature, fish confinement, reservoir host populations, water quality factors, injury, and radiation. The factors were studied singly and in combination, in fish and in the bacterium. In the final analysis, the disease proved to result from a complex interaction between the host, the pathogen,

and the environment. A steady displacement of the coarsefish vector (carrier) population to the Hanford reach of the Columbia River, and a change of virulence in the unaffected carrier, aggravated by temperature elevation and crowding in fish ladders at the new dams, were shown to act in concert to cause these devastating outbreaks of columnaris disease in salmon. In the years following shutdown of the Hanford production reactors, the disease outbreaks continued until operation of the Columbia River dams was eventually modified. Radiation as a causative factor was ineffective in either the bacterium or the fish except at cumulative doses far above any possible exposure to the reactor effluents. A corollary of these studies was the experimental demonstration by Dr. John A. Strand^(a) and colleagues (1977) of tritium suppression of the primary immune response in rainbow trout. How this effect on the fish immune system was differentiated from the effects of the columnaris pathogen is an interesting story (Strand et al. 1982).

Fish populations in the Columbia River ecosystem are besieged by many adversities. Quantifying the relative importance of a single factor in a complex of interwoven factors, all influencing fish populations, is a formidable task, about which more is said in section IV F (Tritium in the Environment).^(b)

In a paper by Templeton and a panel discussion at the Rochester Conference on Environmental Toxicity of Aquatic Radionuclides, some additional generalizations can be approached (Templeton 1976, Miller and Stannard 1976). The abstract of Templeton's paper is given below.

There is some concern that with the expansion of nuclear energy for power the oceans will be subjected to an increasing radiation dose commitment as a result of effluent discharges. This chapter discusses some implications of the present dose commitment and attempts to evaluate the potential effects upon aquatic populations. Experimental studies have indicated the sensitivity of some stages of individual organisms to irradiation, however the dose rates required are many times above that presently existing, even at major waste disposal sites. From a consideration of the role of natural regulatory mechanisms in exploited populations, it would appear that populations of highly fecund species are unlikely to be perturbed by present levels of radiation from controlled disposal to the marine environment. However, for species of low fecundity, additional stress, whether from fishing, irradiation or other pollutants, may decrease their chances of survival. Consideration of potential genetic effects is limited by a lack of quantitative data on radiation-induced genetic changes in aquatic populations. Some limited generalizations are made indirectly from experimental data on other organisms. (Templeton 1976)

The IAEA in Vienna prepared one of its technical report series on the subject of effects of ionizing radiation on aquatic organisms (IAEA 1976b). Its general conclusions are comparable to those of Templeton just quoted. This volume is a concise and handy summary of the field.

The panel discussion at Rochester included remarks by Edward Goldberg to the effect that we have been looking for biological effects of agents such as marine pollutants, e.g., halogenated hydrocarbons, heavy metals, and artificial radionuclides for about twenty-five years and have drawn essentially a blank. Should mega-fish experiments be mounted comparable to the famous mega-mouse genetic experiment at Oak Ridge? There were many at the conference

(a) Dr. Strand is now the manager of the Marine Research Laboratory at Sequim, Washington.

(b) Parts of this and the previous paragraph were supplied by Dr. Vaughan.

who thought we could not learn in any other way, but there were others who were convinced that these populations are all relatively radioresistant, and we would do better to put the effort into studying effects of chemical pollutants to which they may be more sensitive. In fact, the idea was expressed (by Dr. George Berg) that even on conclusion of a large experiment with radioactivity the results might point at some agent far away from radiation or radioactivity as the culprit.

A suggestion made by Richard Foster was to mount studies halfway between the laboratory and the uncontrolled environmental situation. This would involve small lakes, large terrestrial compounds, etc., some of which have already been alluded to. These would be expensive experiments, and much planning would be needed. Only the future will tell if we have the zeal to fund them.

Meanwhile, we must be content with the knowledge that careful investigation has shown it is possible to perturb the environment with radioactivity at high doses, but that effects are not demonstrable at the average doses found in today's environments. Yet, while research on an international scale has been brought to bear on this problem, and the results in "unusual" organisms do not seem greatly at variance with those from the more commonly studied higher vertebrates, we have in no way covered all possibilities. The breeding grounds and habitats, both terrestrial and aquatic, for large sectors of the biosphere cannot be said to have been really thoroughly studied for sensitivity to either radionuclides or chemical toxins. Meanwhile pollution is mounting, some of it in crucial spots.

A suitable summary for this section on effects in ecosystems is one prepared by Whicker and Schultz regarding the effects of chronic irradiation on populations:

Concerning plant communities, stands characteristic of harsh environments and climatic extremes are relatively radioresistant and early seral stage communities tend to be more resistant than following successional stages. Radiosensitivity of plants is related to characteristics of chromosomes and cell populations and to stature and growth form, with the smaller herbaceous plants being more radioresistant than larger, woody species. Vascular species are much more sensitive than thallophytes. Reproduction and productivity may be reduced at reasonably low exposures. At higher exposures, breakdown of community structure can be expected. Alteration of plant community is related to radiation dose rate, time of exposures, radiosensitivity of component populations and to secondary effects and interactions.

With respect to performance of terrestrial animal populations, the process most susceptible to impairment by radiation stress is reproduction. However, some populations that exhibit rapid repopulation potential can often adjust to reduced natality and still maintain stable numbers. On the other hand, longer-lived species with normally low reproductive potential can gradually decline in density to the point of extinction at relatively low chronic exposure rates. Across the animal kingdom, there is a 2 to 3 order-of-magnitude range in innate sensitivity to radiation. Furthermore, the biotic and abiotic environment, as well as many other innate characteristics can significantly alter the response of animal populations to radiation. As a result, the prediction of population response in irradiated ecosystems becomes a very difficult task, unless the exposures are either very low, or very high.

Studies on natural aquatic populations have been limited to systems that have been contaminated with radionuclides to produce dose rates generally less than 1 rad/day. At such levels, the responses of aquatic populations have been very difficult to document and quantify. While genetic mutations have been observed at the chromosome level in organisms subject to such dose levels, the effects on

fecund populations subject to strong selective pressures appear inconsequential. Based on laboratory investigations, developing embryos of fish can be expected to be one of the most sensitive components of aquatic systems to radiation, but there is considerable variation between species, as well as within species, depending on stage of development and environmental factors. (Whicker and Schultz, 1982, Vol 2, pp. 165-166)

It is very likely that other perturbations of the environment deserve a higher priority now than radioactivity. Nevertheless, we can be glad that the attitude of caution developed in the very earliest days has persisted regarding radioactivity, and the ecological community is alert for the presence of any "sleepers."

C. More About Nuclear Power Reactors

We have already reviewed the first major nuclear reactor accident, Windscale, as part of the historical review of the early years. We will consider here some more generic matters and one other specific incident, Three Mile Island. The participants in this work are ubiquitous.

Even though it is clear that mining of uranium ores and fuel reprocessing plants contribute much higher activity levels in *routine* operations than a power reactor, it is the reactor that engenders the most apprehension because of its potential, however remote, for release of very large quantities of radionuclides in a major accident. To evaluate these potentials, much of the biomedical research already discussed in this book had to be brought to bear. Added to that were the special problems of environmental distribution (see for example, Reinig 1970).

Obviously, any biomedical data relating to routine releases from reactors to the environment fall either into the category of computation of doses from measured activity of effluents or of epidemiologic surveys. For calculation of doses to humans, much use has had to be made of the critical pathway and the critical population (critical group) concepts. Probably the most succinct and overt early discussion came from Committee 4 of the ICRP in its Publication 7 (ICRP 1965). It is taken up in detail in chapter 15. It is convenient to choose one or two of the numerous and complex pathways, viz., one(s) that would involve the highest collective dose, or sometimes the highest individual dose, and designate the population involved as the critical population. This may be, for example, a specific occupational group like fishermen or the residents of a particular area with food and/or water from the critical pathway. Then the radionuclide or radionuclides that both pass through that pathway in largest amount and enter the human body most readily can be selected as the critical nuclide(s).

Experience has shown that detailed study of all potential pathways and all potentially critical nuclides is seldom needed. For example, the strontium-plant-cow-milk-child pathway easily takes precedence over others under many conditions. A general diagram of possible critical pathways is given in ICRP 1965.

Once the associated radiation dose has been calculated, the potential risk can be estimated and discharge rates regulated to well below permissible levels. Extrapolations from the research data to operational matters have produced a voluminous literature based almost entirely on computations. The early outlines can be seen in the referenced ICRP publication, while more recent features appear in the numerous Regulatory Guides of the U.S. NRC and predecessor documents under the AEC.

Biomedical research on possible *effects* of routine discharges from nuclear power plants consist primarily of epidemiologic surveys. Many, such as the

Mancuso study of Hanford, concern the combined effects of many sources. Many others are still in progress and will require many years for completion. Still others are still at the feasibility-study stage.

Quite early, Ernest Sternglass, University of Pittsburgh, declared that he had convincing evidence of increased infant mortality around the sites of operating nuclear power reactors. He had already alleged similar effects in cities receiving more than the average amount of fallout from the weapons tests at the NTS. No waiting for a feasibility study here! Since his saga begins with fallout problems and was translocated, essentially intact, to reactor sites, we will discuss both aspects together in chapter 12.

Claims of a similar nature have been made concerning the population living near the Indian Point, New York, nuclear station. Weik (1969) cited at Joint Committee on Atomic Energy (JCAE) hearings increased cancer incidence in the population—unfortunately much too small for either statistical or epidemiologic suitability. Fadeley Cunningham (1965) presented data showing increased malignancy incidence for populations in certain counties of Oregon near the Columbia River and attributed the increase to radionuclides from the Hanford reactors. The flaws in this study were discussed by Stannard (1973b, p. 349).^(a) There have been and will be other such correlations that we will have to leave to the epidemiologists to interpret. Getting an epidemiologically suitable sample is not easy, as we have seen in this book from the radium chapter on.

At the Third Congress of the International Radiation Protection Association there was a series of summaries of radiation doses from various sources, such as natural radiation, medical uses, accidents, and routine operations.

So much for the routine operations. The evaluation of radiation doses and health consequences of a serious accident at a nuclear power reactor has also been almost entirely computational. Only the special field tests, to be described in chapter 14, involved actual measurements "before the fact." All others have been computational or, "after the fact," like Windscale, the Monroe Reactor, Three Mile Island, and others. We will review briefly the gradual development of appreciation for what could be involved in a major reactor accident.

An early review concerned radiation from the passage of a hypothetical cloud of reactor debris (Holland 1956) and came from the U.S. Weather Bureau. Such evaluations of dose from cloud passage have continued under the general title "submersion dose" and appear in the latest ICRP report on radionuclide standards (ICRP 1979). Walter Snyder and his associates at Oak Ridge should be credited with keeping such calculations current and meaningful over many years.

Early analyses of aspects broader than cloud passage alone were made by Parker and Healy at Hanford (1956) and by Marley and Fry from the United Kingdom (1956). These were condensed papers given at the first Atoms for Peace Conference and reflected work that appeared earlier in in-house documents. A still earlier report in terms of publication date came from the Knolls Atomic Power Laboratory in 1954 (Fitzgerald, Hurwitz, and Tanks 1954), but it did not receive as wide distribution.

Probably the first report on large accidental releases to receive widespread general attention in the United States was one prepared by staff at BNL, first as a

(a) For example, certain pertinent counties away from the river were omitted without explanation, age-sex adjustments were inadequate, etc.

laboratory report (BNL 1957), and later published in part in the proceedings of the second Atoms for Peace Conference (Kuper and Cowan 1959). They considered two types of postulated events: release of a fraction of the fission product inventory from a 500-MW (thermal) reactor that had operated for 180 days, and a core meltdown in which the fuel and all of the volatile fission products were released.

At the same international meeting, B. P. Leonard (1959) from Convair presented estimates of the amounts of radioactivity, possible doses, and probable number of people affected in rural and urban environments for either "run-away" or "meltdown" incidents. He took pains to review the influence of meteorological variables and other perturbations and showed that they could make fairly large differences in the outcome.

In both papers, the calculated consequences of the types of accident were catastrophic and created something of an uproar.^(a)

Since these early reports, there has been a constant drumbeat. No one disputes the potential biological effects of the release of any substantial portion of the inventory from a large power reactor. Many laboratories and individuals have devised criteria for the siting of power reactors. For example, an important midyear topical symposium of the Health Physics Society was devoted to nuclear facility siting (Voillequé and Baldwin 1970). Here discussions ran from consideration of building a power plant deep in rock in the city of Stockholm, Sweden, to the idea of never locating a nuclear power plant less than many, many miles from a populated area.

In the next few years, the AEC sponsored and produced more or less continuous studies of possible population doses and design-objective guides not only for reactors, but for the entire nuclear industry. The EPA did likewise for the environmental implications. Most of these entailed estimates of the growth of nuclear power that we now recognize as overestimates. Yet the data and conclusions give a good picture of the activities and thinking of the period.

The reports include WASH-1209 (AEC 1973c) and an earlier preliminary version, WASH-1139 (AEC 1972). This was followed by WASH-1250, a report specifically on the safety of nuclear power reactors and related facilities (AEC 1973d). Each of these focused on the year 2000, and the series has become known as "The Year-2000 Study." The content can be estimated from the titles as given in the bibliography to this chapter.

The EPA's contributions began as an estimate of ionizing radiation doses in the United States in the period 1960-2000 (Klement et al. 1972). This was followed by specific limits for environmental contamination with radionuclides (see chapter 15 for more details).

At this same time, the idea of keeping all exposures "As Low as Reasonably Achievable" (ALARA) came into its own and was blessed by incorporation into a final environmental statement, WASH-1258 (AEC 1973b). Also, Appendix I of the code of Federal Regulations was modified because of environmental pathway findings (chapter 15). A concise summary of the events of this approximately five-year period was produced by Hart (1974).

An even more extensive reanalysis came in 1975 in the Reactor Safety Study, WASH-1400 (AEC 1975), the so-called Rasmussen Report. This multivolume

(a) It is reported that AEC later tried to hush up these worst-case conclusions since the chance of releasing all of the fission products, even in a meltdown, is exceedingly small. Might as well try to hush up a tornado!

document contains much biomedical information, considerably more than some of the earlier reports. Yet, primarily it fine-tunes the implications drawn earlier. The most significant advances were better risk estimates, better evaluation of environmental parameters, and much more information on the actinide elements. We need still more on these. It is clear from this report, however, that the chief problems are engineering ones, i.e., the probabilities that various levels of events could occur. The report is very strong on these, using a "fault-tree" analysis.

The accident at the Three Mile Island nuclear power plant near Harrisburg, Pennsylvania, needs no description here. Fortunately, the environmental radiation levels were never high enough to test any of the calculations referred to above. The collective radiation dose to the population out to fifty miles was estimated at 2,000 person-rem.^(a) Estimated annual collective dose to the same population from natural background radiation was about 240,000 person-rem in the same period. This was true despite the high levels of contamination within the facility.

An interesting environmental measure of possible contamination from the Three Mile Island plant involved measurements of ^{131}I in meadow voles (Field et al. 1981). Thyroids from these animals contained more ^{131}I than normal, and the amount varied among the three sites chosen. The highest (11.4 pCi/thyroid peak, 5.6 pCi/thyroid average) was at site III, the one predicted to show the highest concentrations by the DOE. None of these were alarming, but the work resulted in the vole being proposed as a monitoring organism for ^{131}I contamination of ecosystems.

Some very real biomedical effects took place, but they were not radiation effects. As stated by Fabrikant (1981), (director of the Public Health and Safety Task Force of the President's Commission on the Accident at Three Mile Island, now domiciled at the Donner Laboratory in Berkeley and the Department of Radiology at the University of California, San Francisco), there were real effects on the mental health of the people living in the region and the workers at the plant. These patterns of anxiety, confusion, and sometimes paranoia showed a relation to distance somewhat like a conventional dose-response pattern.

It should be clear that biomedical research has developed ample information to assay and predict the effects of large accidental releases from nuclear power reactors. The effects of routine releases still remain with the problems of the low-dose realm. The engineering problems and the true probabilities of accident-causing defects remain in much need of further diligent investigation.

D. The Liquid Metal Fast Breeder Reactor Program

In the early 1970s, there were indications that the world's supply of uranium might be insufficient to meet the expected demands for electricity from nuclear power. The idea of a breeder reactor, under discussion for a considerable period, received additional impetus at this time. For various technical reasons,

(a) There are those who point out that this average figure is not meaningful. The maximum individual dose could have been higher. This cannot be denied. The measurement resources were too strained and the circumstances too hectic. Would that they had enlisted the cooperation of the population as the British did at Windscale to get more individual and early measurements.

cooling by liquid sodium was preferred over cooling by water or air, and a cycle that bred mostly plutonium was favored. However, the possible amounts of plutonium and of other transuranics formed were enormous. Add to this the chemical and explosion hazards of liquid sodium at high temperature, the need for extremely careful planning and analysis of such an installation became quite apparent.

About mid-1973, a massive environmental impact statement (EIS) (see later section and chapter 16) was undertaken, which involved every aspect of the transuranics. It brought in every laboratory with expertise in the field. All of the toxicological research on plutonium and other transuranic elements we have reviewed in earlier chapters was brought together, including yet another analysis of the "hot particle" problem in lung. Hearings were held with many volumes of testimony; some of it directed at the entire uranium fuel cycle. The monumental EIS for the Liquid Metal Fast Breeder Reactor (LMFBR), WASH-1535 (AEC 1974), contains almost all anyone could want to know about what had been done about transuranics and their hazards. The big gap concerned their behavior in the environment. This was partly because most of the information had been obtained from desert environments, like the NTS, or very specialized environments like the Pacific Proving Grounds.^(a) Since the site chosen for the LMFBR was on the Clinch River near Oak Ridge, Tennessee, the lack of ecological information on transuranics applicable to a humid forested environment was apparent.

The AEC gathered an environmental team to develop a research program to fill in the gaps and to further expand our knowledge of the cycling of transuranic elements in all environments. This involved HASL in New York, the environmental group from the NTS, including the Nevada Applied Ecology group whose work we will review in chapter 14, the Lawrence Livermore Laboratory, PNL (Hanford), the University of Washington fisheries group, the UCLA Atomic Energy Project, and the Woods Hole Oceanographic Institution. The areas of immediate concern are as outlined in figure 11.13, taken from the foreword written by R. L. Watters (1980) to the recent volume prepared for DOE, *Transuranic Elements in the Environment* (Hanson 1980).

The listing is, of course, comprehensive for the short term. There was already considerable information on some of the topics, as a perusal of recent symposia, such as the one held by the IAEA in San Francisco (IAEA 1976a), testifies. It even included a modicum of work in humid environments such as that at the Savannah River Plant. However, there were special concerns for the longer term as described by Watters below:

The areas of research just mentioned are of immediate concern, but beyond these near-term considerations are those related to the possible long-term persistence of the transuranic elements in available form on the scale of hundreds and thousands of years. Such considerations are very difficult to address adequately with contemporary research. However, two approaches are under way which may provide reasonable first approximations to the prediction of long-term behavior. One is the theoretical approach to studying the chemical and physical processes in soil of those radionuclides with the objective of developing good thermodynamic data. We need information on the equilibrium concentrations of the various oxidation states in different environments, on complexation processes, and on diffusion

(a) A few others such as Palomares, Spain, and Thule, Greenland, were involved also (chapter 14).

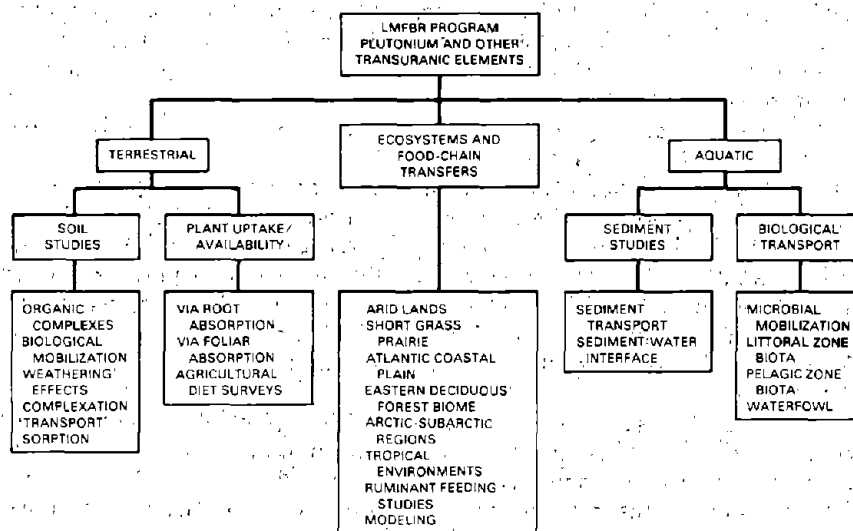


FIGURE 11.13. United States Department of Energy, Office of Health and Environmental Research, transuranium elements research program. (Redrawn from Watters et al. 1980.)

coefficients for various species. We can then apply this type of information to predictive modeling. An empirical approach would be to study the distribution and environmental behavior of naturally occurring elements that have properties analogous to those of the transuranium elements. For instance, the availability for plant uptake of the rare earth neodymium, which has been subjected to weathering for thousands of years, may provide a basis for predicting the uptake of americium after long periods of time because americium and neodymium have quite similar chemical and physical properties. Other rare earths, uranium, and thorium are also candidates as analogs for some of the transuranic elements in environmental studies. (Watters 1980)

A further indication of the extent of the effort engendered by the potential for an LMFBR is the fact that workshops involving all aspects were held in Estes Park, Colorado, in July 1974 and in Seattle in November 1975. Hanson (1980, p. vii) states that environmental aspects of research on transuranic elements expanded sixfold between these two meetings. Incidentally, the second workshop was the basis not only for the book edited by Hanson, but the grand review of all of actinide biology in 1977 discussed in chapter 8. There was a third workshop in April 1977 held at Woods Hole, Massachusetts. It did not produce the same enthusiasm as the first and second.

Since the Hanson volume is something of a landmark, its table of contents is reproduced at the end of this chapter (note 4).

As is well known, the LMFBR has not been built. It may never be built. Despite the reassurances regarding potential health effects, the idea of a plutonium economy with problems far wider than potential biomedical ones has engendered extreme caution. Nevertheless, the environmental aspects were so very thoroughly analyzed on paper that a short summary appears worthwhile.

This is given below based in part on a clear and concise summary prepared by N.F. Barr of ERDA (Barr 1976) for the IAEA symposium already cited. These give a clear idea of the wide range of disciplines and expertise that had to be brought to bear.

First, the potential amounts of transuranic elements that might be released, i.e., the "Source Term," had to be estimated. This had to be put in terms of the electrical energy produced, since no one knew how many megawatts or gigawatts might be produced. The dominant source for routine operations was expected to be releases from the fuel reprocessing plants, not the LMFBR itself. This was estimated at 1 mCi of alpha-emitting transuranics per 1,000 MWe/yr with all other sources at factors of ten or more lower. The composition of the releases was based on the composition of high burn-up fuel and was assumed to exist as small airborne particles with an activity median diameter (chapter 9) of $0.3 \mu\text{m}$.

This release rate was estimated to be one part in 10^9 of the materials present. In other words, it assumed containment was good to one part in a billion, stated to be an already accomplished fact technologically.^(a)

The next step was estimation of what fraction of the released material would find its way into humans. For *direct* inhalation, an assumed particle size distribution of the inhaled fraction was taken as 5×10^{-6} . This figure was based on model meteorological conditions for the north central part of the United States. It is that portion that would be inhaled *before* the material reached the ground. In addition to this, wind would pick up some of the material after deposition on the ground and resuspend it. This is represented by a resuspension factor (chapter 15) and is larger initially than it is later on, since the material tends to become fixed with time, be carried to less superficial portions of the soil, etc. The initial resuspension factor was taken as 10^{-5} , with decrease to a constant minimum value of 10^{-9} on a half-life of fifty days. Combining this postdeposition pickup with the amount initially inhaled resulted in an estimate that about 10^{-5} of any amount of transuranic released would reach humans by the inhalation route if exposure were indefinitely long.

The ingestion pathway of most import, based upon laboratory and field studies, was taken as plant material. It was assumed that the released transuranics were uniformly distributed on the soil surface and that the plant material reached a concentration of one-tenth of that in the soil. The fraction absorbed from the gastrointestinal tract was taken as 0.3×10^{-5} for plutonium and 10^{-3} for americium and curium, following ICRP figures. It was calculated that the ingestion pathway made a negligible contribution immediately after release but that it could reach 10^{-2} of the amount released eventually (i.e., over the rest of time).^(b)

The next step was calculation of radiation dose equivalents. These used the techniques described in chapter 20 and throughout the literature. For

- (a) This was for routine operations. There was more uncertainty regarding contributions of "off-normal" operations. It was expected these could be checked out when the facilities were designed, built, and operated. This very uncertainty may have contributed to the reluctance to proceed with the program.
- (b) Because of the indications that plutonium and other transuranics may become more transportable with time in the environment, a contributing factor from ingestion of as high as 10^{-1} of the amount deposited was indicated by Barr (1976) as being used. However, this was not clearly revealed in the EIS.

inhalation, the integrated seventy-year dose equivalent was approximately 1 mrem/pCi (10^{-12} Ci) of transuranic inhaled. Combined with similar dose equivalent calculations for ingestion, an estimate was made of potential health effects. This was couched in terms of the risk of developing cancer (pulmonary, skeletal, or liver) and of genetic defects. The risk estimates came from the NAS-NRC (BEIR) reports and the United Nations (UNSCEAR) documents (chapter 16). Most of the total risks were in the realm of 0 to 10^{-4} to 10^{-3} probability per 1,000 MWe year. (Total probability of cancer ran from a minimum of 0 to a maximum of $380 [138-1,045] \times 10^{-6}$ and that of genetic defects at genetic equilibrium from a minimum of 24×10^{-6} to a maximum of 600×10^{-6} .)

The above is a very incomplete description of the monumental discourses and detailed calculations that went into evaluation of the LMFBR. It is probably the largest compilation of its kind ever undertaken. It is reviewed here for its intrinsic interest and to show the extent to which prospective planning can be brought to bear on the health aspects of a major enterprise. It is ironic that all of this concerns a facility that has not yet been built and may never be built. Thus, the validity of many of the engineering assumptions may never be tested. The validity of the biomedical data is being tested constantly by the ongoing research programs in the radionuclide field. Of these, obviously, some of the environmental parameters are the most uncertain. Unfortunately, and despite the very sizeable inflow of new information, there is now little motivation for investigators or administrators to return to the LMFBR modeling and correct or modify it on the basis of new results. We will have to obtain that information by other means.

As would be expected with so complex an enterprise, there are dozens of parameters that had to be based on insufficient or poor evidence. Sometimes the figures chosen may have overestimated the eventual risk. Indeed, there was a tendency to choose the more conservative alternatives. Yet, there were many figures that had to be largely guesses and may have been underestimates.

Naturally, there were many critics ready to challenge each assumption. Since the overall risk estimates were close to what is gradually becoming the neighborhood of acceptable overall risks, any major changes in the LMFBR model parameters could move the estimated risk into an unacceptable realm. Perhaps the most frequently challenged figures were related to engineering, e.g., the true ability to maintain a containment factor of 10^{-9} . Yet, the biomedical parameters came in for their share of challenges too.

This tremendous effort did two things, at least, for the biomedical research with transuranics: (1) it brought together a large portion of the published and unpublished literature in the field; and (2) it made apparent that, despite our progress, the story is far from complete, and research, both field and laboratory, cannot be relaxed.^(a)

(a) Alternative technologies were, of course, under consideration. Some had what appeared to be considerably reduced biomedical implications. One of these was the high temperature gas cooled reactor (HTGR), which could be made into a breeder. Till (1976) gives a lucid description of the two fuel cycles involved, ^{235}U HTGR fuel and LMFBR fuel, and compares their potential toxicity on recycling. Many steps, such as toxicity of the fuel itself, as well as radiological insult to aquatic plants, invertebrates, fish, and terrestrial animals dependent on aquatic food supplies showed from some to considerable factors favoring HTGR fuel. Nevertheless, Till concludes that, once

It is unfortunate that this major compendium is not likely to be easily available in future years, since such documents have a tendency to go into limbo when the project is completed or found to be impractical.

E. Transuranics in the Environment

The above discussion of the LMFBR leads to a brief general discussion of transuranic elements in the environment. All four of the chapters on radionuclides and the environment consider work with the transuranic elements such as plutonium, americium, curium, etc. in many contexts. Other chapters have addressed their biological effects in individual organisms.

It all started, of course, with the initial studies centered around the Hanford plant. It continued with many special tests and events that we will discuss in chapter 14. The field began a general crescendo in numbers of laboratories and investigators in the early 1970s. The eleventh Hanford biology symposium held in September 1971 and entitled *The Biological Implications of the Transuranium Elements* had a series of presentations on environmental aspects (Thompson and Bair 1972). These included aquatic and terrestrial environments, plants, dairy foods, and critical environmental parameters in plutonium-safety evaluations.^(a) At about the same time, Rudolph, Carroll, and Davidson (1971) at Battelle Columbus Laboratories issued an annotated bibliography entitled *Plutonium and Its Effects in the Environment—A Selected Literature Survey*. This work covers much more than environmental studies. Indeed, most of the "effects" citations come from laboratory experiments.

In the same year, the Los Alamos Scientific Laboratory held an environmental plutonium symposium (Fowler, Henderson, and Milligan 1971). This included an excellent and much-quoted summary of the entire field by Wright Langham (Langham 1971); a discussion of the distribution of plutonium from accidents and field experiments by Harry Jordan (see chapter 14); consideration of methodology and analytical techniques by people from HASL; the EPA laboratories in Las Vegas and in Montgomery (Alabama), as well as Los Alamos, and industry; evaluation of airborne reconnaissance methods with a device known as the FIDLER (Field Instrument for Detection of Low Energy Radiation) (chapter 14);

released to terrestrial and aquatic environments, the two fuels apparently have about equal radiotoxicity. He urges further research to evaluate the potential radiobiological and ecological impact of the uranium fuel used for the HTGR. This author can find little evidence that this is being done. This may be because when the HTGR becomes a breeder it produces plutonium, and the differences between the potential input of the two fuels in the environment is further diminished. There is still the question of relative engineering safety of the HTGR, reputed to be greater than that of the LMFBR, but that is not an appropriate subject for this book.

- (a) The invited paper by Noshkin (from Woods Hole at that time) considers ecological aspects of the dissemination of plutonium and other transuranics in aquatic environments (Noshkin 1972). It gives a very complete summary table of ^{239}Pu concentrations and concentration factors in marine invertebrates and algae in various parts of the world, average concentration factors in several tissues of marine vertebrates, and the plutonium profile in bottom sediments. There are marked species differences. The paper by Romney and Davis from UCLA gives a similar review for ecological aspects of plutonium in terrestrial environments (Romney and Davis 1972). They remark on the relative paucity of information and describe the organization and objectives of the Nevada Applied Ecology Group (see chapter 14).

Detection of Low Energy Radiation) (chapter 14); plutonium in surface soil at Hanford; concentrations in some marine organisms; and air transport of plutonium at Rocky Flats. The symposium was closed by a review paper from Jack Healy on some of the problems of resuspension (chapters 14, 15).

Stannard (1973a) wrote a general review of plutonium in the environment as part of the large volume entitled *Uranium, Plutonium, Transplutonic Elements*, cited several times previously.

The American Nuclear Society organized a special session on "Environmental Levels of the Transuranium Elements" at its winter meeting in October 1974. The program for this is reproduced below:

Invited speakers for the "Environmental Levels of the Transuranium Elements" session at the American Nuclear Society Winter Meeting, Washington, D.C. October 30, 1974:

Chairman: Leon Leventhal, LFE Environmental Analysis Laboratories, Richmond, California 94804

1. "Quantitative Health Estimates of Transuranic Releases," Dr. Nathaniel Barr, DBER, US AEC, Washington, D.C.
2. "Toxicity of the Transuranium Elements with Special Emphasis on Plutonium," Dr. J. Newell Stannard, University of Rochester, School of Medicine, Rochester, New York
3. "Analytical Considerations Connected with the Transuranium Element," R. A. Wessman, K. D. Lee, W. J. Major, and L. Leventhal, LFE Environmental, Richmond, California
4. "Transuranics in the Marine Environment," Dr. Vaughan T. Bowen, Woods Hole Oceanographic Institute, Woods Hole, Massachusetts
5. "Transuranium Elements in the Atmosphere," C. W. Thomas and R. W. Perkins, Battelle, Pacific Northwest Laboratories, Richland, Washington
6. "Transuranium Elements on Land," Dr. J. H. Harley, US AEC, HASL, New York, New York
7. "Transuranium Nuclides in the Environment From Management of Solid Radioactive Waste," G. H. Daly and Anthony S. Kluk, DWMT, US AEC, Washington, D.C.

(HASL-29, April 1, 1975)

Each of the papers was a review and summary of how things stood in late 1974.

At about this time came the very large expansion of institutions and workers in the field engendered by the plans for an LMFBR as already described (section D 8). This spawned not only the large report described for the LMFBR, but a large IAEA symposium held in San Francisco in November 1975^(a) and numerous other special meetings on transuranics in the environment (not necessarily from LMFBR operations).

The IAEA symposium proceedings begin with an introductory address by James Liverman, the director of the Division of Biological and Environmental Research in ERDA, and are filled with individual reports on plutonium in aquatic and terrestrial environments in many parts of the world, biological uptake and transfer, pathways to humans, and environmental monitoring and evaluation.

At about this time, an independent summary on the international scene came from the Department of Radiation Physics at the University of Lund, Sweden. Elis Holm (1977) prepared a compact monograph whose primary purpose was

(a) IAEA 1976a.

discussion of the transuranics in the unique food chain characteristic of high northern latitudes: lichen-reindeer-man. We will consider this pathway further in chapters 12 and 15. However, it included a useful broad discussion of the sources of transuranics and their relations to other components of fallout. The monograph also takes up methodologies in some detail and reprints papers from the same group on plutonium in Mediterranean surface waters.

The Rochester International Conference on the Environmental Toxicity of Aquatic Radionuclides (Miller and Stannard 1976) also placed much emphasis on transuranics. Edward Goldberg from Scripps Institution of Oceanography proposed a global monitoring program for transuranics based on the use of two "sentinel" organisms, mussels and barnacles. W.O. Forster from the Division of Biomedical and Environmental Research of ERDA discussed the ERDA research programs, summarized source terms for transuranics, and discussed how to deal with various isotopes of plutonium, using the specific activity concept. J. N. Miettinen from Helsinki, Finland, described plutonium food chains with particular emphasis on the lichen-reindeer-man sequence and on an aquatic food-chain, sediment-benthic fauna-fish. Edgington and colleagues from Argonne National Laboratory described plutonium behavior in the Great Lakes, also with many data on food chains. (They found some very large concentration factors in plankton.) J. A. Hetherington from the U.K. Ministry of Agriculture, Fisheries and Food, whose work we met in connection with Windscale, described the behavior of plutonium nuclides in the Irish Sea. Livingston and Bowen from the Woods Hole Oceanographic Institution described behavior of americium in the marine environment and how it compares to plutonium. We have already mentioned the work on a pond ecosystem at Hanford described in that volume by Emery and Klopfer.

Finally, we have at hand for ready reference the book edited by Hanson (1980) and already quoted in earlier sections. An especially useful chapter for our present purposes is a "Synthesis of the Research Literature" by Watters et al. (1980). This contains tables and diagrams with referencing sufficient to provide a very succinct, yet complete, review of the field as it stood at the time of publication.^(a)

The primary thrust of the transuranic problems has, in recent years, gone more and more toward the problems of waste disposal. Much of the most pertinent work took place after the theoretical cutoff date for this book. However, something should be said about it.

The U.S. NAS-NRC has had a blue-ribbon committee working on waste disposal problems for many years. The Department of Energy and the EPA have devoted considerable attention and resources to the issues and possible technical solutions (DOE 1981; EPA 1981). This includes draft standards from the EPA. Of course, the NRC has formulated licensing and other requirements (NRC 1981). Very recently, the NCRP convened a task group of its committee on waste disposal (chaired by Merrill Eisenbud) to review criteria for the disposal of transuranium waste. A preliminary report from this task group (NCRP 1982) provides a handy review of the issues and makes recommendations somewhat contrary to those being developed by the regulators. For example, they state that radium in the environment behaves so differently from plutonium that establishment of

(a) Space precludes incorporation here of the very useful tabulations, but it is hoped the interested reader will have no difficulty in obtaining the publication, since it is recent and published by the DOE Technical Information Center.

a limit for transuranics based on analogy to radium is invalid. Further, they suggest that no single limit for waste concentration can be supported. Instead, site-specific pathway models should be employed using "thorough and comprehensive" studies of site-specific conditions.

We will close this section by quoting the summary from the synthesis by Watters et al. (1980) in the book by Hanson:^(a)

The preceding discussion leads to a number of generalizations that can be summarized as follows:

1. The nature of the source for release to the environment is important in the initial deposition and distribution of transuranic elements. However, as environmental factors, such as erosion, weathering, and biological processes proceed, the original chemical and physical properties are altered and source influence diminishes.
2. The major repositories of plutonium and americium are soils and sediments.
3. Suspended particles in air and water act as vectors for the physical movement of plutonium and americium, and erosional processes are the principal means of translational movement in the environment.
4. In spite of the large fraction of plutonium and americium residing in soils and sediments, chemical and biological processes produce a very small fraction of soluble species in terrestrial and aquatic environments. These species are incorporated in biological tissue, but the concentrations in biota have not produced demonstrable deleterious radiation effects.
5. An increase or decrease in the soluble fraction of plutonium over long weathering times cannot be demonstrated at this time. However, preliminary observations of naturally occurring analog elements indicate that plant uptake and transfer of plutonium and americium through food chains would not be expected to change appreciably over time.^(b)
6. Concentrations of plutonium do not increase from one trophic level to the next in natural food webs except for sorption by phytoplankton and one observation of starfish feeding on mussels.
7. The environmental chemistry of transuranic elements in marine and in oligotrophic freshwater systems is similar in a number of ways. However, significant differences in chemical species exist in many lakes where chemical conditions, such as pH and ligand concentration (both organic and inorganic), may be different.
8. Present levels of transuranium elements in our environment have not produced discernible ecological effects.

We will see examples of the types of work leading to these conclusions as we proceed through these chapters on the environment.

F. Tritium in the Environment

In chapter 10, we engaged in a detailed consideration of tritium and its compounds as a possible inhalation hazard. We also considered briefly the possibilities for transmutational effects at the cellular and whole-organism level. In chapter 20, we will consider the potential for effects of tritium when it is combined into important biomolecules. Yet, despite all of this coverage, the considerable effort expended in ascertaining how tritium behaves in the

(a) As indicated earlier, the complete table of contents of this book is given as note 4 at the end of this chapter.

(b) This conclusion must be regarded as still moot.

environment needs reviewing as a special topic here. This holds, even though the effort has brought few surprises.

The research and field results show, as expected, that tritium is widely disseminated and very transportable in general. If there were not so much tritium produced in the nuclear fuel cycle, probably much less attention would have been paid to understanding its behavior in the environment. However, with megacuries produced and few processes available for efficiently sequestering it permanently, it would not take a very large concentration factor in the environment to develop potentially significant doses. Therefore, a considerable effort was made, and that is the subject of this section. The workers and laboratories are primarily those we have already met.

Global levels of tritium and its compounds obviously increased during the years of atmospheric weapons testing, especially when fusion devices were involved. The nuclear fuel cycle makes its contribution of tritium and its compounds largely from reprocessing plants and certain types of reactors, especially those moderated with heavy water (e.g., in Canada).

In the early days (1950s, early 1960s), discussions of environmental contamination from radionuclides seldom singled out tritium. Strontium, cesium, etc., came in for much more attention. The programs for both of the Atoms for Peace Conferences in the 1950s have little on tritium, much more on strontium and cesium. While the earlier annual reports from the laboratories, e.g. Hanford, describe experiments on individual organisms and point out such phenomena as the oxidation of tritium by bacteria, uptake by bean roots, and the like, the orientation was only obliquely environmental. Even the first major symposium on radioisotopes in the biosphere (Caldecott and Snyder 1960) did not devote an identifiable section to tritium, partly because the discussions were mostly generic and not oriented toward specific radionuclides.^(a)

At the first National Radioecology Symposium (section IV), there was a review from the University of Connecticut Marine Research Laboratory called "Tritium in Ecology" (Skauen 1963). This was part of a section recording the role of several radionuclides in ecology. It considered geology, bacteriology, zoology, botany, and work with man but did not do much integrating of the subject. It does show, however, by the listing of 155 titles in the bibliography, that the subject was beginning to attract attention.

It appears that the U.S. PHS may have led off significant general interest in tritium in the environment *per se* as contrasted to individual organisms. It started with the expected expansion of the nuclear power industry. Peterson et al. from the Bureau of Radiological Health presented estimates of environmental contamination with tritium up to the year 2000 at an IAEA symposium in Vienna (Peterson et al. 1969). Before long, such reports became numerous since the PHS operated a tritium surveillance network, and others followed. Data included tritium from nuclear reactors, nuclear testing, fuel reprocessing, waste disposal, etc. The possible public health significance of the known and postulated releases in the opinion of Peterson et al. (1969) follows:

(a) One of the reasons for the slow start with tritium is that its production in nuclear fission, in contrast to being an activation product, was not fully appreciated until the later 1950s (Albenesius 1959; Albenesius and Ondrejcin 1960).

7.0 Public Health Significance

The principal form of tritium in reactors is tritiated water and conventional concentration processes such as ion exchange and evaporation do not remove appreciable amounts of tritium from liquid effluents. For this reason, tritium may comprise between 50 and almost 100% of the total activity in reactor discharges to the environment. The Radioactivity Concentration Guide (RCG) for tritium, however, is much higher than for most common fission products. The RCG for tritium is 10^{-3} $\mu\text{Ci/ml}$ and because of its short biological half-life (12 days), its low disintegration energy, and uniform distribution in the body, its relative health significance is smaller than for other fission products such as ^{90}Sr and ^{137}Cs .

The estimated tritium release from a 1000 MW(e) pressurized-water reactor is approximately 7000 curies per year (average of Table V). Plants employing single-pass condenser systems to remove excess heat have circulation rates of about 1.5×10^{15} cm^3 per year and the resulting concentration would be about 5×10^{-6} $\mu\text{Ci/ml}$ or 0.5% of the RCG for exposure of the general population (10^{-3} $\mu\text{Ci/ml}$). The volume of water discharged from reactors employing cooling towers is considerably smaller and may be only 2000 gallons per minute. Under these circumstances the effluent concentration could approach 20% of the guideline value. Under certain circumstances it may be necessary to restrict discharges or to provide supplementary dilution for these plants.

The Public Health Service operates a tritium surveillance network in the United States to provide information on nationwide trends and tritium concentrations in water downstream from large nuclear installations. The results reported by this network are published periodically. Present levels are 0.2-10 nCi/l and the dose contribution from the maximum concentration has been estimated to be less than 1.6 mrem/year.

The buildup of tritium in small confined bodies of water may approach concentrations approximately 20% of the RCG which suggests that environmental surveillance would be indicated to monitor this accumulation. Our predictions for Lake Michigan show that the tritium concentrations in the Lake will be about 40 nCi/l, most of which will be contributed by the reactors on the Lake. Continuous consumption of this water for a fifty-year period would result in a total integrated dose of only 350 mrem, which is considerably less than that from natural radiation sources. (Peterson et al. 1969. Reference citations have been omitted.)

Pressures for a more comprehensive review of all aspects of tritium, including its environmental behavior, were mounting in and out of Washington. Soon the AEC sponsored a critical review of tritium sources and its behavior in the environment. It was written by Jacobs and published in 1968 (see references for chapter 10). The AEC also sponsored, with the EPA, a large symposium held in Las Vegas in 1971 edited by Moghissi and Carter and published in 1973.

One of the questions in the investigators' minds was still, "Will tritium show a positive concentration factor comparable to those seen for many other radionuclides in the environment?" The answer is not simple, but several papers at the symposium shed light on the subject.

A review by Bruner from AEC (1973) compared specific activities of samples of many invertebrate organisms (including separated out "bound" and "free" portions of tritium) to similar data from the hydrosphere. He concluded that invertebrates in general do not enrich the organic fractions of their tissues with tritium from the environment. (Specific activities varied with time depending on the amount of fallout present.) A puzzling exception to this generalization was the water flea, *Daphnia*. It showed a ratio between dry tissue and tritiated food of over four. However, the roster of organisms surveyed by Bruner included phytoplankton, zooplankton, mollusks, water plants, and other flora and insects,

and there were no other exceptions. Several even showed what appeared to be discrimination against tritium.

Other papers at this symposium and a general literature review done slightly earlier by Elwood (1971) made it clear that most of the tritium (as tritiated water) is distributed rapidly and uniformly throughout the body water of animals and approaches equilibrium with the environmental concentration in a few hours. In plants, it usually takes longer to reach equilibrium. In both cases, a small fraction can be bound to organic molecules either directly or by entering the system from the environment in bound form. This portion, of course, has a much longer retention time than unbound tritium. Thus, the chemical form at the time of arrival makes a real difference, as discussed by Kirchmann et al. (1973) but not necessarily to the extent needed to support a positive concentration factor.

By contrast, Cohen and Kneip (1973) from New York University, working around the Indian Point pressurized water reactor on the Hudson River estuary reported tritium concentrations (in picocuries per liter) in sediment ten times higher than in the ambient water, four times higher in fish, and three times higher in rooted aquatic plants. They were well aware that such an apparent concentration factor might reside in part in varying concentrations of the discharge and the fact that the system was not in a steady state. Indeed, the authors postulated an "inheritance" of organically labeled compounds as a possible mechanism for accumulation of tritium in biota above ambient concentrations.

Concentration factors may not be as important to know in the case of tritium as uptake and transfer rates and retention factors. The group at Lawrence Livermore Laboratory has expended much effort in obtaining such factors. At the tritium symposium, Koranda and Martin (1973)^(a) studied the movement of tritium in soil systems from the Sedan shot^(b) crater at the NTS and also in an experimental cornfield near Livermore, using tritium injected into the soil beneath the plants at different depths. It was clear that the half-life of tritium in soil is longer than in most other components of the ecosystem.

The Livermore people also looked at tissue-water and tissue-bound tritium in plants exposed to tritiated water vapor and measured uptake coefficients and retention determined over both short- and long-term exposures. The three component retention curves described for vertebrates in chapter 10 were seen in the plant material studied.

The work was extended to ecosystems in a tropical rain forest of Puerto Rico and the passage through small mammals over several generations in the Sedan crater (Jordan et al. 1970; Martin et al. 1970; Martin and Koranda 1971).

The conclusions were that tritium movement in ecosystems is complex. Many different compartments seem to be involved. On balance, however, rapid movement^(c) of the bulk of the tritium is as characteristic of environmental receptors as of the animals described in chapter 10, with always a small but significant fraction in bound form.

(a) Many of the reports from Livermore cited in this section appeared also, sometimes in greater detail, as UCRL reports.

(b) One of the "Plowshare" shots—chapter 14.

(c) Koranda and Martin give half-times in plants as generally shorter than in animals, in contrast to the conclusions of Elwood cited above. The differences are not large, however.

Turning to aquatic systems, the Lawrence Livermore investigators (Harrison, Koranda, and Tucker 1973) studied uptake of tritium in an artificial marine pool by clams, crabs, and fish. The kinetics of uptake and loss showed rapidly and slowly exchangeable fractions in all soft tissues and permitted construction of a model to predict changes in tissue-bound tritium with changes in exposure concentrations.

The modeling was extended to calculation of the dose to man (Moghissi, Patzer, and Carter 1973), via food-chain transfer to man (Anspaugh et al. 1973), and to a model for calculating guidance for limiting environmental releases of tritium on the basis of the calculated dose to man (Rohwer, Kelly, and Booth 1973). For the latter, a system known as "CUEX"^(a) was developed, which we will consider in connection with the Plowshare project.

John Strand and William Templeton, at PNL, examined the possibility of the late effects from tritium radiation on embryogenesis,^(b) using the fertilized eggs of rainbow trout. In a series of studies (Strand et al. 1973, 1977, 1982; Strand, Templeton, and Tangen 1971; Strand, Templeton, and Olson 1976; and Strand and Thompson 1976), they and their colleagues conclusively showed that the primary immune response in this fish species was suppressed at 4-rad doses after challenge with the ubiquitous fish pathogen, *Flexobacter columnaris*. The dose-response curve was exponential from 0.04 to 40 rad, indicating that these effects could be reliably extrapolated to the lower dosages. Their studies are interesting in that the 4-rad dose corresponded to a 20-day exposure to the then-accepted maximum permissible concentration (MPC) of 0.1 $\mu\text{Ci}/\text{ml}$. Secondary challenge of the fish, seventeen months later, showed that the impairment was irreversible, although the dose levels are considerably higher than one would expect to find environmentally. Strand examined other features, also, such as growth, developmental abnormality, mortality, and evidence for tritium accumulation ratios in excess of 1.0. With the exception of immune suppression, no other significant findings were noted.^(c)

In 1977, the EPA developed very broad projections concerning environmental contamination with radionuclides, including tritium (EPA 1977).

The next large crop of pertinent reports on tritium in the environment came in 1979 and 1980. Of primary interest are the NCRP report, *Tritium in the Environment* (NCRP 1979), the IAEA symposium on the Behavior of Tritium in the Environment (IAEA 1979b), and an experts' report to the Nuclear Energy Agency (NEA) of the Organization for Economic Cooperation and Development (NEA 1980). The NCRP report is an especially concise and readable summary with full documentation. The IAEA symposium contained individual papers from worldwide sources.^(d) The NEA review provides useful comparative data for four radionuclides that distribute in the environment as gases or as airborne particles, viz., tritium, ^{14}C , ^{85}Kr , and ^{129}I .

The NCRP report reiterates the presence of at least three pools for tritium in individuals, with half-lives as described in chapter 10. They add to this information three different compartmental models for the environment. There is a simplistic one-compartment model comprising the circulating waters of the world

(a) Cumulative Exposure Index.

(b) Remember the similar work on rodents in the laboratory done by Cahill (chapter 10).

(c) This paragraph supplied by Dr. Burton Vaughan.

(d) The table of contents of this symposium appears as note 5 at the end of this chapter.

with which man maintains equilibrium. Using a dose-rate factor of 0.095, μrad for 1 pCi/l/yr, the tissue dose rate from a megacurie-per-year release is calculated worldwide and also to the Northern Hemisphere and to the area between latitudes 30° and 50° north. A more realistic three-compartment model considers the atmosphere, land surface, and ocean surface waters. The same type of calculations for dose rate are made. Finally, a complex seven-compartment model with the needed additional transfer coefficients is given. This adds deep groundwater, deep ocean water, surface soil water, and saline lakes and inland seas to the compartments of the three-component model.

For each model, it was necessary to estimate the volume of each compartment and the mean residence time (volume divided by the rate of entrance into and egress from the compartment). The dose rates per megacurie released are all in the microrad-per-year range and are roughly comparable between the three-compartment and seven-compartment models, but considerably lower on a world basis with the one-compartment model. These very low dose rates are consistent with what has been said about tritium already from individual dose calculations. However, we should not forget that very large amounts of tritium can be released in an active nuclear fuel cycle, and tritium cannot be disregarded, as Gofman has stated (1981).

By the time of the NCRP report, the question of whether or not a significant concentration factor exists for tritium had been resolved in the negative. What appeared earlier as concentration processes were considered by the NCRP committee to be due to differences in residual specific activity of certain tissues and organs, particularly some with high concentrations of liquid and fat. Since these were still well below the specific activity of the tritiated water from which the deposit was derived, no true concentration process was considered to be involved. In view of the large amounts of tritium potentially invading the biosphere, it is fortunate that concentration factors such as those seen with many radionuclides such as the actinides do not exist.

The IAEA symposium devoted over seven hundred pages to tritium in the environment and thus cannot help but emphasize the level of interest and effort attracted to the subject on an international scale. Many of the reports concern behavior in individual organisms and have already been mentioned in chapter 10. Much of the work concerns releases from various nuclear facilities. Some concern laboratory investigations, particularly with aquatic organisms in both fresh- and salt-water ecosystems, including several we have already discussed (White Oak Lake, Savannah River Estuary, Irish Sea). Some are mechanistic and concern movements in soil, the atmosphere, plants, and trees, and some concentrate on analysis of pathways. The distribution among countries, laboratories, and subjects is very broad, as is indicated by the table of contents of this symposium (with country of origin added) as shown in note 5.

Somewhat unexpected were the potential tritium releases to the environment from consumer products such as radioluminous compounds in paint or plastic and electrical and electronic devices.^(a) Wehner (1979) estimated that an expected liberal exemption policy for the construction and disposal of such devices could lead to cumulative doses in excess of those from the nuclear power industry, at least in the Federal Republic of Germany. Combs and Doda

(a) As we saw in chapter 10, tritium gradually took over from ^{226}Ra in the luminous paint industry because of the health problems with radium.

(1979) from the U.S. NRC indicated that one million curies (1 MCi) of tritium were distributed in 1977 for backlighting the liquid crystal displays in digital electronic watches. This can be compared to 3 MCi from power reactors and 6 MCi produced naturally. Thus, the NRC feels that careful environmental study of the production, and especially the disposal, of these consumer products is necessary.

We will close this consideration of tritium in the environment with a brief discussion of the NEA experts' report (NEA 1980). As indicated, the report considers ^{14}C , ^{85}Kr , and ^{129}I as well as tritium. It is a very handy summary of the source terms for each, assessment of radiation doses for these radionuclides when emitted to the environment, the maximum dose equivalents to the most exposed individuals, collective dose equivalent commitments, and matters of management and cost-effectiveness. The membership is shown at the end of this chapter (note 6).

Of most interest at this point is the comparison of maximum dose and of collective dose equivalent commitment^(a) for these four mobile radionuclides when emitted to the environment. Figures 11.14A and B show these calculated figures. The number of terms and complex models needed to arrive at figures like those given above is very large.^(b) The fact that it can be done with a modicum of assurance (the uncertainties are still large, as indicated in a special section of the report) attests to the great amounts of information accumulated for environmental behavior as well as dosimetry of these substances.

It is of interest that the local exposure from the fuel reprocessing plant was the largest for all four isotopes in terms of the maximum dose equivalent rates, while the heavy water reactor contributed the most in the case of both tritium and ^{14}C when collective dose equivalent commitment is calculated. It is also noteworthy that the boiling water reactor is the lowest of the group in dose associated with tritium.

In chapter 15, we will have an opportunity to look in somewhat more detail at the environmental pathway assumptions and data that go into making calculations such as those resulting in figure 11.14A and B.

G. The Environmental Impact Statement

We will review historically the genesis of the EIS in chapter 16. Enactment of the National Environmental Policy Act (NEPA) by the U.S. Congress was specifically triggered by plans to build a nuclear power plant on Chesapeake Bay, and AEC and ERDA had to meet the requirements of the act. We have just considered some aspects of the report, WASH-1535 (AEC 1974, 1975), the environmental impact statement for the LMFBR program. While this may be one of the most voluminous and most thoroughly discussed and reviewed of such statements, many others are almost as comprehensive and detailed. They changed the

(a) Dose equivalent commitment times the population size.

(b) Pamela Bryant from the U.K. National Radiological Protection Board apparently spearheaded this review for the NEA. She produced a very broad paper to lead off an IAEA symposium in 1979. This includes the modeling for tritium, ^{14}C , ^{85}Kr , and ^{129}I . For tritium, the regional populations included were around Lakes Erie and Ontario and the St. Lawrence River, the Northeast Irish Sea, and the Baltic Sea. For the other nuclides, fewer sample populations were included. This presentation (Bryant 1979) is an important complement to the NEA document.

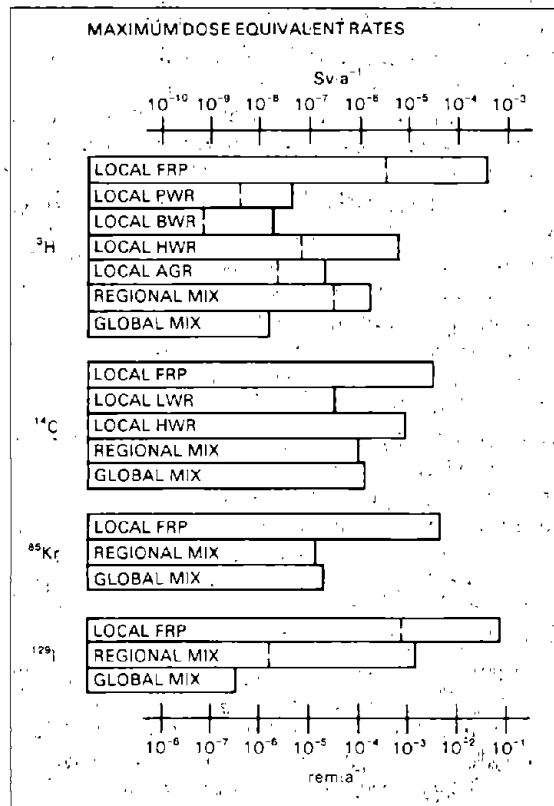
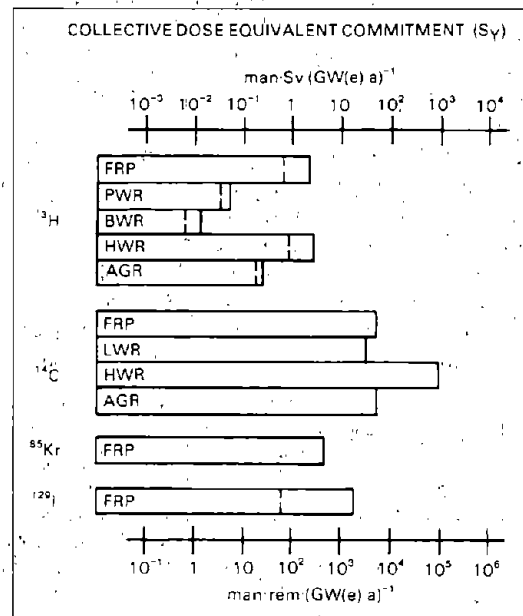


FIGURE 11.14A. (Left) Values of the maximum dose rates from four principal radionuclides to the most exposed individuals from local, regional and global sources. Emissions of tritium from reactors are to both hydrosphere and atmosphere; other emissions are to atmosphere only. Total emissions of tritium and ^{129}I from FRPs to salt water in particular regions are estimated to result in the local and regional maximum dose rates shown by the dashed lines. The components of the maximum dose rates from tritium emitted totally to salt water at reactors are also shown by dashed lines (from NEA 1980).

FIGURE 11.14B. (Right) The collective dose-equivalent commitments, in Sv, for four radionuclides that can be avoided by complete retention and isolation for 10^4a of radionuclides that would otherwise be emitted. Emissions are to the atmosphere except for tritium from reactors for which emissions to both the atmosphere and hydrosphere have been assumed. The dashed lines show the estimated commitments avoided if emissions of tritium and ^{129}I from particular facilities are totally to sea water (from NEA 1980).

FRP = Fuel Reprocessing Plant
PWR = Pressurized Water Reactor
BWR = Boiling Water Reactor
HWR = Heavy Water Reactor
AGR = Advanced Gas-Cooled Reactor
a = Annum
Gw(e) = Gigawatt Electrical



entire mechanism by which environmental concerns were accommodated in the planning process.^(a)

The growing need to prepare these statements galvanized much action in environmental research and in the projection of population doses from multifarious activities.^(b) Each statement bears theoretically on a specific site and process or set of processes. In the early phases, very careful analyses were made of meteorology, geology, ecology, hydrology, etc. of the specific site concerned. As the pressures rose, many statements became more generic in nature. They used the characteristics of the site, but many of the underlying calculations, such as population dose, became more or less standardized. Thus, the research and development efforts described in the earlier sections of this chapter that had become more or less generic were brought to bear on a variety of environmental impact statements in a variety of settings.

The existence of these large repositories of information must be noted and readers informed that they will find in these documents much of specific interest to research on the health effects of radionuclides. There is no doubt that the need for the EIS underscored the research information that was needed and stimulated new projects, even though the amount of new information from one EIS to the next is not large.

VII. Summary and Commentary

This chapter, the first of five concerned with research bearing on radionuclides in the environment, has reviewed what was almost another new dimension—the work around the major production sites.

It began with the very early concern for the fisheries in the Pacific Northwest that developed when the decision was made to locate the plutonium production reactors on the Columbia River at Hanford, Washington. The first work was done in the early 1940s at the Applied Fisheries Laboratory of the University of Washington, even before the Hanford reactors were built. It extended to studies on the river itself and the development of an ecology group at Hanford. This group eventually worked with terrestrial contamination problems as well as those in the aquatic environment. It was a large and significant effort that resulted in learning much about the radiobiology of salmon and trout, the fact that the pile effluents were toxic primarily because of chemical toxins released rather than the radioactivity, and the broad conclusion that the operation of the plant had not had, nor would it be expected to have, a significant deleterious effect on the fisheries of the Pacific Northwest. We associate with this work the names Lauren Donaldson, Allyn Seymour, Arthur Welander, and others at the University of Washington; Richard Foster, Jerry Davis, Wayne Hanson, Harry Kornberg and associates at Hanford. This was the only substantive environmental research (as compared to monitoring) done around the sites during World War II.

(a) While the edict of Congress and the enactment of NEPA caused a review of plans for the Calvert Cliffs Plant on Chesapeake Bay, many ecologists regard the voluminous tome prepared for the proposed "Operation Chariot" in Alaska (in later chapters) as the first full-blown de novo environmental impact statement.

(b) An important criterion is whether or not the proposed activity is "major" or "federal." Guidance on such decisions is available in, for example, the book by Heer and Hagerty (1977). Most of the activities we are considering are both "major" and "federal."

Soon after World War II, the contamination of White Oak Lake stimulated the development of a small ecology group at Oak Ridge. The development was pushed by Karl Morgan, head of the Health Physics Division, and it grew under the tutelage of Stanley Auerbach into a large and prestigious ecology program. While there was considerable interest in the aquatic system of White Oak Lake and the Clinch River, the Oak Ridge effort involved much terrestrial as well as aquatic ecology.

While Hanford and Oak Ridge were the original sites with substantive ecology programs, many others developed in the postwar years. Some of these were outgrowths of local site-specific problems (Brookhaven, Idaho Falls, Rocky Flats, Savannah River); others had a broader base (Colorado State University, Health and Safety Laboratory in New York, Lawrence Livermore, Los Alamos, New York University, the University of California at Los Angeles, and others). One result of this activity was the designation of a new specialty—radioecology. The genesis and development of the field and the contents of the major symposia associated therewith are described in the chapter.

The number and variety of organisms studied were greatly expanded by the need to do environmental studies. Plant systems and aquatic forms came in for much more attention than in the laboratory-oriented investigations. Furthermore, ecosystems entered the picture and have proven to be one of the more difficult aspects of the field. Probably the ecosystem approach needs more attention in the future than any other aspect. Yet, it is a complex and expensive enterprise. The chapter has questioned whether or not we are prepared to do what is really needed.

The chapter concludes with a review of some special topics whose origins can be traced to the work around the production sites. These include marine radioecology, possible effects of radionuclides in ecosystems, consideration of site-specific problems around nuclear reactors, transuranic nuclides in the environment, and prospective studies such as the Liquid Metal Fast Breeder program.

It was around the production sites that the field of radioecology was born. If the chapter does nothing else, it should make it apparent that concern for the environmental impact of the production of radionuclides was a top priority from the earliest days and that any mistakes that were made must be chalked up to lack of knowledge and not to crass disregard for the environment.

Note 1—Contents of First National Symposium on Radioecology^(a)

Introductory Speaker

Impact of Atomic Energy on the Environment and Environmental Science—
John N. Wolfe

I. General Review Papers

Radiation Effects and Peaceful Uses of Atomic Energy in the Plant and Soil Sciences—John D. Spikes

Radiation Effects and Peaceful Uses of Atomic Energy in the Animal Sciences: Radiation and Biologic Capability—Paul S. Henshaw

Continental Close-in Fallout: Its History, Measurement and Characteristics—Kermit H. Larson

(a) Schultz and Klement (1963).

Disposal of Radioactive Wastes: Its History, Status and Possible Impact on the Environment—Donald W. Pritchard and Arnold B. Joseph

II. Cycling and Levels of Radionuclides in the Terrestrial Environment

Some Effects of Environmental Factors Upon Accumulation of World-Wide Fallout in Natural Populations—J. J. Davis, W. C. Harrison and D. G. Watson

Vegetational Analyses in a Creosote Bush Community and Their Radioecologic Implications—William H. Rickard

Biological Availability of Strontium-90 to Small Native Animals in Fallout Patterns from the Nevada Test Site—J. W. Neel and K. H. Larson

The Dynamics of Fallout Distribution in a Colorado Alpine Tundra Snow Accumulation Ecosystem—William S. Osburn, Jr.

Accumulation of Strontium-90 in Yearling Columbian Black-Tailed Deer, 1950-1960—Vincent Schultz and William M. Longhurst

Environmental Pathways of Radioactive Iodine from Nuclear Tests in Arid Regions—Norman R. French and K. H. Larson

Accumulation and Cycling of Organic Matter and Chemical Constituents during Early Vegetational Succession on a Radioactive Waste Disposal Area—H. R. DeSelm and R. E. Shanks

Factors Related to Concentration of Radiocesium in Plants Growing on a Radioactive Waste Disposal Area—R. E. Shanks and H. R. DeSelm

Movement and Accumulation of Radiostrontium and Radiocesium in Insects—D. A. Crossley, Jr.

Estimation of Dose Rate and Equilibrium State from Bioaccumulation of Radionuclides by Mammals—Stephen V. Kaye and Paul B. Dunaway

Experimental Isolation of Food Chains in an Old-Field Ecosystem with the Use of Phosphorus-32—Eugene P. Odum and Edward J. Kuenzler

Analog Computer Models for Movement of Nuclides through Ecosystems—Jerry S. Olson

Cycling of Cesium-134 in White Oak Trees on Sites of Contrasting Soil Type and Moisture. I. 1960 Growing Season.—John P. Witherspoon, Jr.

III. Cycling and Levels of Radionuclides in the Marine Environment

Cycling and Levels of Strontium-90, Cerium-144 and Promethium-147 in the Atlantic Ocean—Vaughan T. Bowen and Thomas T. Sugihara

Gross Beta Radioactivity in Marine Organisms—Thomas W. Hatfield, Donald M. Skauen and John S. Rankin, Jr.

Radionuclides in Plankton and Tuna from the Central Pacific—F. G. Lowman

Radioactivity of Marine Organisms from Guam, Palau and the Gulf of Siam, 1958-1959—Allyn H. Seymour

Zinc-65 in Oysters in Fishers Island Sound and Its Estuaries—Bryant W. Fitzgerald and Donald M. Skauen

Experimental Studies of the Turnover of Phosphate in Marine Environments—Lawrence R. Pomeroy

Qualitative Distribution of Radionuclides at Rongelap Atoll—E. E. Held

Availability of Sediment-Sorbed Materials to Marine Biota—T. W. Duke, E. R. Ibert and K. M. Rae

Micro-organisms in Environments Contaminated with Radioactivity—James B. Lackey and Carrie F. Bennett

The Role of Phytoplankton in the Cycling of Radionuclides in the Marine Environment—T. R. Rice

The Uptake, Accumulation and Exchange of Strontium-90 by Open Sea Phytoplankton—E. F. Corcoran and J. F. Kimball, Jr.

The Effect of Environmental Ions on the Concentration of Radiocalcium and Radiostrontium by Euryhaline Teleosts—Sidney J. Townsley

IV. **Cycling and Levels of Radionuclides in the Freshwater Environment**

The Strontium and Calcium Relationships in Clinch and Tennessee River Mollusks—D. J. Nelson

The Fate of Radiostrontium in a Freshwater Community—Ivan L. Ophel

Translocation of Phosphorus in a Trout Stream Ecosystem—Robert C. Ball and Frank F. Hooper

Natural Radioactivity in the Food Web of the Banded Sculpin *Cottus carolinae* (Gill)—W. L. Minckley, J. E. Craddock and L. A. Krumholz

Radium in Natural Waters in the United States—Robert C. Scott

V. **Effects of Ionizing Radiation on Plants and Animals in Terrestrial Environments**

Ecological Effects of Ionizing Radiation on Organisms, Communities and Ecosystems—Robert B. Platt

Prediction of the Sensitivity of Plants to Chronic Gamma Irradiation—Arnold H. Sparrow and George M. Woodwell

Changes in a Herbaceous Plant Community During a Three-Year Period Following Exposure to Ionizing Radiation Gradients—Frank McCormick

A Study of Succession in Fields Irradiated with Fast Neutron and Gamma Radiation—Charles P. Daniel

Effects of Radiation from an Air-Shielded Reactor on Forest Litter Production—John T. McGinnis

The Effect of Ionizing Radiation on *Smilax* with Special Reference to the Protection Afforded by Their Production of Underground Vegetative Structures—Hedley G. Chappell

Effects of Ionizing Radiation on *Pinus taeda* L.—Robert A. Pedigo

Factors Affecting Tree Seed and Seedling Radiosensitivity—Margaret B. Heaslip

Recovery of Vegetation on Atomic Target Areas at the Nevada Test Site—Lora Mangum Shields and Philip V. Wells

Radiation Dosages in the Vicinity of an Unshielded Nuclear Reactor—James J. Cowan and Robert B. Platt

Influence of Four Rocky Mountain Regional Environments on Pea Plants Grown from Irradiated Seeds—William S. Osburn, Jr.

Natural Radiation Effects of Vertebrate Animals Inhabiting the Uranium Areas of Southeastern Utah—Wilmer W. Tanner

Comparative Ecological Studies of Animals at the Nevada Test Site—Donald M. Allred and D. Elden Beck

Effects of Ionizing Radiation on Mammal Populations on the White Oak Lake Bed—Paul B. Dunaway and Stephen V. Kaye

The Effect of Neutron-Gamma Radiation on Free-Living Small Mammals at the Lockheed Reactor Site—Jay H. Schnell

Relative Sensitivity of Nestlings of Wild Passerine Birds to Gamma Radiation—William K. Willard

VI. Effects of Ionizing Radiation on Plants and Animals in Marine and Freshwater Environments

Increase in Radioresistance of Fish to Lethal Doses with Advancing Embryonic Development—Kelshaw Bonham and Arthur D. Welander

Effect of Chronic Feeding of Sr^{90} - Y^{90} on Rainbow Trout—R. E. Nakatani and R. F. Foster

The Effects of Continuous, Sub-lethal Gamma Radiation on the Intrinsic Rate of Natural Increase and Other Population Attributes of *Daphnia pulex*—J. S. Marshall

The Preliminary Investigation of Salivary Gland Chromosomes of *Chironomus tentans* Fabr. from the Clinch River—D. J. Nelson and B. G. Blaylock

Effects of Uranium Mill Wastes on Biological Fauna of the Animas River (Colorado-New Mexico)—J. B. Anderson, E. C. Tsivoglou and S. D. Shearer

Exploratory Study of Radiation Damage in the Thyroids of Coral Reef Fishes from the Eniwetok Atoll—Aubrey Gorbman and Miriam S. James

VII. Ecological Techniques Utilizing Radionuclides in Terrestrial Environments

Radioactive Tracers as an Aid to the Measurement of Energy Flow at the Population Level in Nature—Eugene P. Odum and Frank B. Golley

Tracer Studies of the Breakdown of Forest Litter—J. S. Olson and D. A. Crossley, Jr.

Methods for Introducing Radionuclides into Plants—T. W. Sudia and A. J. Linck

Consumption of Vegetation by Insects—D. S. Crossley, Jr.

Use of Radionuclides in Ecological Studies of Insects—Dale W. Jenkins

The Role of Radionuclides in Insect Behavior Studies—Claude H. Schmidt and Carroll N. Smith

Techniques for Studying Movements of Vertebrates in the Field—John R. Tester

A Method of Measuring Waterfowl Dispersion Utilizing Phosphorus-32 and Zinc-65—W. C. Hanson and A. C. Case

Use of the Jack Rabbit as a Bio-indicator of Environmental Strontium-90 Contamination—Z. M. Fineman, R. McBride and J. Detmer

VIII. Ecological Techniques Utilizing Radionuclides in Marine and Freshwater Environments

Biological and Physical Transport of Radionuclides in Stratified Lakes—Arthur D. Hasler and Gene E. Likens

Use of Light Nuclides in Limnology—Edward S. Deevey, Jr., Minze Stuiver and Nobuyuki Nakai

Evaluation of the Carbon-14 Technique for Measurement of Primary Production—M. B. Allen

Use of Nitrogen-15 for Measurement of Rates in the Nitrogen Cycle—John C. Neess, Richard C. Dugdale, John J. Goering and Vera A. Dugdale

Zinc-65 in Studies of the Freshwater Zinc Cycle—Roger W. Bachmann

IX. The Occurrence, Effect and Utilization of Nuclides in the Environment

Manganese in Ecology—Peter J. Wangersky

Biological and Environmental Behavior of Ruthenium and Rhodium—S. I. Auerbach and J. S. Olson

Reactions of Tungsten in Soils and Its Uptake by Plants—E. M. Romney and J. D. Childress

The Radioecology of Calcium—Sidney C. Hsiao

Factors Controlling the Distribution of the Rare Earths in the Environment and in Living Organisms—Ralph F. Palumbo

Cesium and Its Relationships to Potassium in Ecology—J. J. Davis

Review and Discussion of Barium—Norman R. French

Iron and Cobalt in Ecology—F. G. Lowman

Environmental Behavior of Chromium and Neptunium—Richard F. Foster

Some Aspects of the Biology of Zirconium-95—Edward E. Held

Iodine in the Environment—W. C. Hanson

Tritium in Ecology - A Review—Donald M. Skauen

The Natural Radioactive Series in Organic Material—F. F. Koczy

Arsenic and Its Radioisotopes in the Environs—R. L. Junkins

Review of Zinc in Ecology—T. R. Rice

Plutonium, Its Biology and Environmental Persistence—J. H. Olafson and K. H. Larson

APPENDIX

Panel Discussion on Education and Research Training—Eugene P. Odum, Moderator

Bibliography A—Alfred W. Klement, Jr., and Vincent Schultz

Bibliography B—Alfred W. Klement, Jr., and I. E. Wallen

Note 2—Literature Reviews of Specific Radionuclides in the Environment^(a)

Auerbach, S. I. and Olson, J. S., Biological and environmental behavior of ruthenium and rhodium, in *Radioecology*, Schultz, V. and Klement, A. W., Jr., Eds., Reinhold, New York, 1963, 509.

Bittel, R., Bibliographic Discussion of the Physico-Chemical Behavior and the Radioecology of Ruthenium in Hydrobiological Systems (in French), Rep. CEA-Bib-123, Commissariat à l'Energie Atomique, Centre d'Etudes Nucleaires, Fontenay-Aux-Roses, France, 1968; *Nucl. Sci. Abstr.* 22(24), 51486.

(a) From Whicker and Schultz (1982), Vol. 2, pp. 205-206.

- Bittel, R., Bibliographic Discussion of the Physico-Chemical Behavior and the Radioecology in Hydrobiological Systems of Cerium and Other Lanthanides (in French), Rep. CEA-Bib-138. Commissariat à l'Energie Atomique, Centre d'Etudes Nucleaires, Fontenay-aux-Roses, France, 1969; *Nucl. Sci. Abstr.* 23(21), 43715.
- Clajus, P., Ecology of Radium. A Literature Survey (in German), Rep. SAAS-183, Staatliches Amt fuer Atomsicherheit und Strahlenschutz, Berlin, German Democratic Republic, 1975; *Nucl. Sci. Abstr.* 33(6), 12009.
- Crowson, D. L., Man-made tritium, in *Tritium*, Moghissi, A. A. and Carter, M. W., Eds., Messenger Graphics, Phoenix, Ariz., 1973, 23; *Nucl. Sci. Abstr.* 28(11), 27223.
- Davis, J. J., Cesium and its relationships to potassium in ecology, in *Radioecology*, Schultz, V. and Klement, A. W., Jr., Eds., Reinhold, New York, 1963, 539.
- Elwood, J. W., Ecological aspects of tritium behavior in the environment, *Nucl. Saf.*, 12(4), 326, 1971.
- Foster, R. F., Environmental behavior of chromium and neptunium, in *Radioecology*, Schultz, V. and Klement, A. W., Jr., Eds., Reinhold, New York, 1963, 569.
- Francis C. W., Plutonium mobility in soil and uptake in plants: a review, *J. Environ. Qual.*, 2(1), 67, 1973.
- Francis C. W., Radiostrontium Movement in Solids and Uptake in Plants, U.S. DOE Rep. TID-27564 (DOE Critical Review Series), U.S. Department of Energy, Washington, D.C., 1978.
- French, N. R., Review and discussion of barium, in *Radioecology*, Schultz, V. and Klement, A. W., Jr., Eds., Reinhold, New York, 1963, 557.
- Hakanson, T. E., Environmental pathways of plutonium into terrestrial plants and animals, *Health Phys.*, 29 (4), 583, 1975.
- Hanson, W. C., Iodine in the environment, in *Radioecology*, Schultz, V. and Klement, A. W., Jr., Eds., Reinhold, New York, 1963, 581.
- Hanson W. C., Ecological considerations of the behavior of plutonium in the environment, *Health Phys.*, 28(5), 529, 1975.
- Hanson, W. C., Ecological considerations of natural and depleted uranium, in *The Natural Radiation Environment III*, Vol. 2, Gesell, T. F. and Lowder, W. M., Eds., U.S. DOE Rep. CONF-780422, U.S. Department of Energy, Washington, D.C., 1980.
- Held, E. E., Some aspects of the biology of zirconium-95, in *Radioecology*, Schultz, V. and Klement, A. W., Jr., Eds., Reinhold, New York, 1963, 577.
- Hsiao, S. C., The radioecology of calcium, in *Radioecology*, Schultz, V. and Klement, A. W., Jr., Eds., Reinhold, New York, 1963, 525.
- IAEA, Tritium and Other Environmental Isotopes in the Hydrological Cycle, Tech. Rep. Ser. No. 73 (Publ. STI/DOC/10/73), International Atomic Energy Agency, Vienna, 1967.
- Jacobs, D. G., Sources of Tritium and its Behavior Upon Release to the Environment, U.S. AEC Rep. TID-24635, U.S. Atomic Energy Commission, Washington, D.C., 1968.
- Junkins, R. L., Arsenic and its radioisotopes in the environs, in *Radioecology*, Schultz, V. and Klement, A. W., Jr., Eds., Reinhold, New York, 1963, 615.
- Kirk, W. P., ⁸⁵Kr: A Review of the Literature and an Analysis of Radiation Hazards, U.S. EPA Rep. NP-19251, Eastern Environmental Radiation Laboratory, 1972.
- Koczy, F. F., The natural radioactive series in organic material, In *Radioecology*, Schultz, V. and Klement, A. W., Jr., Eds., Reinhold, New York, 1963, 611.
- Lowman, F. G., Iron and cobalt in ecology, in *Radioecology*, Schultz, V. and Klement, A. W., Jr., Eds., Reinhold, New York, 1963, 561.
- Moiseyev, A. A. and Ramzaev, P. B., Cesium-137 in the Biosphere (in Russian), Atomizdat, Moscow, 1975; *Nucl. Sci. Abstr.*, 33(11), 25998.
- Nishita, H., A Review of Behavior of Plutonium in Soils and Other Geologic Materials, U.S. NRC Rep. NUREG/CR-1056, U.S. Nuclear Regulatory Commission, Washington, D.C., 1979.
- Noshkin, V. E., Ecological aspects of plutonium dissemination in aquatic environments, *Health Phys.*, 22(6), 537, 1972.
- Olafson, J. H. and Larson, K. H., Plutonium, its biology and environmental persistence, in *Radioecology*, Schultz, V. and Klement, A. W., Jr., Eds., Reinhold, New York, 1963, 633.

- Palumbo, R. F., Factors controlling the distribution of the rare earths in the environment and in living organisms, in *Radioecology*, Schultz, V. and Klement, A. W., Jr., Eds., Reinhold, New York, 1963, 533.
- Parfenov, Yu. D., Polonium-210 in the environment and in the human organism, *At. Energy Rev.*, 12(1), 75, 1974.
- Price, K. R., A review of transuranic elements in soils, plants, and animals, *J. Environ. Qual.*, 2(1), 62, 1973.
- Rice, T. R., Review of zinc in ecology, in *Radioecology*, Schultz, V. and Klement, A. W., Jr., Eds., Reinhold, New York, 1963, 619.
- Romney, E. M. and Childress, J. D., Reactions of tungsten in soils and its uptake by plants, in *Radioecology*, Schultz, V. and Klement, A. W., Jr., Eds., Reinhold, New York, 1963, 521.
- Romney, E. M. and Davis, J. J., Ecological aspects of plutonium dissemination in terrestrial environments, *Health Phys.*, 22(6), 551, 1972.
- Schell, W. R. and Watters, R. L., Plutonium in aqueous systems, *Health Phys.*, 29(4), 589, 1975.
- Skauen, D. M., Tritium in ecology—a review, in *Radioecology*, Schultz, V. and Klement, A. W., Jr., Eds., Reinhold, New York, 1963, 603.
- Templeton, W. L., Dosimetry and ecological effects of transuranics in the marine environment, in *Transuranic Elements in the Environment*, U.S. DOE report DOE/TIC-22800, Hanson, W. C., Ed., U.S. Department of Energy, Washington, D.C., 1980, 714.
- Volchok, H., Bowen, V., Dyer, R., Forster, W., Herring, J., Perkowski, J., Rice, T., and Stannard, J., Transuranic elements in *Assessing Potential Ocean Pollutants*, National Academy of Sciences, Washington, D.C., 1975, 27.
- Wangersky, P. J., Manganese in ecology, in *Radioecology*, Schultz, V. and Klement, A. W., Jr., Eds., Reinhold, New York, 1963, 499.
- Whicker, F. W., Ecological effects of transuranics in the terrestrial environment, in *Transuranic Elements in the Environment*, U.S. DOE Rep. DOE/TIC-22800, Hanson, W. C., Ed., U.S. Department of Energy, Washington, D.C. 1980, 701.

Note 3—Participants in Clinch River Study

Oak Ridge National Laboratory
Tennessee Valley Authority
Tennessee Stream Pollution Control Board
Tennessee Game and Fish Commission
U.S. Geological Survey
U.S. Public Health Service

Note 4—Contents of *Transuranic Elements in the Environment*^(a)

FOREWORD

PREFACE

ACKNOWLEDGMENTS

CONTRIBUTORS

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(a) W. C. Hanson, Ed. (1980).

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References

- Åberg, B. and F.-P. Hungate, eds. 1967. *Radioecological concentration processes*. Proceedings of an symposium held in Stockholm, April 25-29, 1966. Oxford-London-New York: Pergamon Press.
- AEC. See Atomic Energy Commission.
- Albenesius, E. L. 1959. Tritium as a product of fission. *Phys. Rev. Letters* 3:274-75.
- Albenesius, E. L. and R. S. Ondrejcin. 1960. Nuclear fission produces tritium. *Nucleonics* 18(9):100.
- Alverson, D. L. 1972. Bioenvironmental features: An overview. Chapter 34 in Pruter and Alverson 1972, pp. 845-57.

- American Chemical Society. 1970. *Radionuclides in the environment*. A symposium sponsored by the American Chemical Society, April 1-3, 1968. E. C. Freiling, chairman. Advances in Chemistry Series, 93. Washington, D.C.: American Chemical Society.
- Anderson, J. B., E. C. Tsivoglou, and S. D. Shearer. 1963. Effects of uranium mill wastes on biological fauna of the Animas River (Colorado New Mexico). In Schultz and Klement 1963, pp. 373-83.
- Anspaugh, L. R., J. J. Koranda, W. L. Robison, and J. R. Martin. 1973. The dose to man via food-chain transfer resulting from exposure to tritiated water vapor. In Moghissi and Carter 1973, pp. 405-22.
- Atomic Energy Commission. 1972. *Nuclear power, 1973-2000*. WASH-1139 (72). Washington, D.C..
- Atomic Energy Commission. 1973a. *Environmental monitoring at major U.S. Atomic Energy Commission contractor sites—Calendar year 1973*. WASH-1259 (73). [One of a series.] Washington, D.C.
- Atomic Energy Commission. 1973b. *Final environmental statement concerning proposed rule making action: Numerical guides for design objectives and limiting conditions for operation to meet the criteria "as low as practicable," for radioactive materials in light-water-cooled nuclear power reactor effluents*. WASH-1258, vol. 1, The statement. Washington, D.C.
- Atomic Energy Commission. 1973c. *The potential radiological implications of nuclear facilities in the Upper Mississippi River Basin in the year 2000—The year 2000 study*. WASH-1209. Washington, D.C.
- Atomic Energy Commission. 1973d. *The safety of nuclear power reactors (light water cooled) and related facilities*. WASH-1250. Washington, D.C.
- Atomic Energy Commission. 1974. *Draft environmental statement [March 1974] and final environmental statement [December 1974] on Liquid Metal Fast Breeder Reactor Program*. WASH-1535. Washington, D.C.
- Atomic Energy Commission. 1975. *Reactor safety study—An assessment of accident risks in the U.S. commercial nuclear power plants*. U.S. Nuclear Regulatory Commission-WASH-1400 (NUREG-75/014). [Prepared under the direction of N. C. Rasmussen, Massachusetts Institute of Technology, with contributions from many people and organizations. A main report occupies one volume, and the several volumes of appendices include an analysis of comments on the draft version of the report.]
- Auerbach, S. I. 1970. Ecological considerations in siting nuclear power plants: The problem of long-term biotic effects. In Foreman 1970, pp. 29-44.
- Auerbach, S. I. 1979. Taped interview at Oak Ridge, Tenn., April 19, 1979.
- Auerbach, S. I. and J. S. Olson. 1963. Biological and environmental behavior of ruthenium and rhodium. In Schultz and Klement 1963, pp. 509-19.
- Auerbach, S. I. and V. Schultz. 1962. *Onsite ecological research*. TID-16890. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Auerbach, S. I., D. J. Nelson, S. V. Kaye, and D. E. Reichle. 1971. Ecological considerations in reactor power plant siting. In IAEA 1971, pp. 805-20.
- Auxier, J. A. and R. O. Chester. 1973. *Report of the Clinch Valley study*. ORNL-4835. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Barr, N. F. 1976. The radiological significance of transuranium radioisotopes released to the environment during operation of the LMFBR fuel cycle. In IAEA 1976b, pp. 649-56.
- Beasley, T. M., L. A. Ball, J. E. Andrews III, and J. E. Halverson. 1981. Hanford-derived plutonium in Columbia River sediments. *Science* 214:913-15.
- Bebbington, W. P. 1973. *Nuclear operations and the environment*. DPSPU 72-30-9. Aiken, S.C.: E. I. du Pont de Nemours and Company, Atomic Energy Division.
- Becker, C. D. and M.P. Fujihara. 1978. *The bacterial pathogen, Flexobacter columnaris and its epizootiology among Columbia River fish. A review and synthesis*. Monograph no. 2. Washington, D.C.: American Fisheries Society.
- BNL. See Brookhaven National Laboratory.
- Brookhaven National Laboratory. 1957. *Theoretical possibilities and consequences of major accidents in large nuclear power plants*. WASH-740. Washington, D.C.: U.S. Atomic Energy Commission.

- Brown, R. E., D. W. Pearce, W. deLaguna, and E. B. Struxness; J. H. Horton, Jr. and C. M. Patterson. 1959. Experience in the disposal of radioactive wastes to the ground. In *Progress in nuclear energy*, ser. 12, pp. 556-65. New York-London: Pergamon Press.
- Bruner, H. D. 1973. Distribution of tritium between the hydrosphere and invertebrates. In Moghissi and Carter 1973, pp. 303-14.
- Bryant, P. M. 1979. Review of radionuclides released from the nuclear fuel cycle and methods of assessing dose to man. In *Biological implications of radionuclides released from nuclear industries*, STI/PUB/522, vol. 1, pp. 1-25. Proceedings of a symposium held in Vienna, March 26-30, 1979. Vienna: International Atomic Energy Agency.
- Bustad, L. 1960. Radioisotopes and environmental circumstances: Significance of nuclear energy effluents in animal populations. Chapter 17 in Caldecott and Snyder 1960.
- Caldecott, R. S. and L. A. Snyder, eds. 1960. *Radioisotopes in the biosphere*. Proceedings of a symposium held in Minneapolis, October 19-23, 1959. Minneapolis, Minn.: Univ. of Minn., Center for Continuation Study.
- Carbon, M. W. and W. A. Houlberg, eds. 1970. *Proceedings of a student conference on nuclear power and the environment*, held at the Univ. of Wisc., April 3-4, 1970. Madison: Univ. of Wisc.
- Carter, M. 1979. Taped interview at Georgia Institute of Technology, April 10, 1979.
- Chamberlain, A. C., J. F. Loutit, R. P. Martin, and R. S. Russell. 1956. The behavior of I^{131} , Sr^{89} and Sr^{90} in certain agricultural food chains. In *Proceedings of the international conference on the peaceful uses of atomic energy*, vol. 13, pp. 360-63. Held in Geneva, August 8-20, 1955. New York: United Nations.
- Cohen, L. K. and T. J. Kneip. 1973. Environmental tritium studies at a PWR power plant. In Moghissi and Carter 1973, pp. 623-39.
- Colorado Committee for Environmental Information. 1970. *Dow Rocky Flats fire: Implications of plutonium releases to the public health and safety*. Subcommittee on Rocky Flats, Boulder, Colo.
- Comar, C. L. and S. L. Hood. 1953. The role of atomic energy in agricultural research. In *Proceedings of the 4th annual Oak Ridge summer symposium*, TID-5115, pp. 481-82. Held in Oak Ridge, Tenn., August 1952.
- Combs, F. and R. J. Doda. 1979. Large-scale distribution of tritium in a commercial product. In IAEA 1979a, pp. 93-99.
- Craig, H. 1957. *Isotopic tracer techniques for measurement of physical processes in the sea and the atmosphere*, publ. 551. Washington, D.C.: National Academy of Sciences-National Research Council.
- Crick, M. J. and G. S. Linsley. 1982. *An assessment of the radiological impact of the Windscale reactor fire, October 1957*. NRPB-R135. U.K., Chilton: Natural Radiological Protection Board.
- Crick, M. J. and G. S. Linsley. 1983. *An assessment of the radiological impact of the Windscale reactor fire, October 1957*. NRPB-R135, addendum.
- Crossley, D. A., Jr. 1963. Movement and accumulation of radiostrontium and radiocesium in insects. In Schultz and Klement 1963, pp. 103-05.
- Cuddihy, R. G., W. C. Griffith, and R. O. McClellan. 1979. Internal review for Office of Environment, U.S. Department of Energy.
- Cushing, C. E., Jr., ed. 1976. *Radioecology and energy resources*. Ecological Society of America special publ. no. 1. Proceedings of the 4th national symposium on radioecology held at Oreg. State Univ., May 12-14, 1975. Stroudsburg, Pa: Dowden, Hutchinson & Ross, Inc.
- Davis, J. J. 1963. Cesium and its relationships to potassium in ecology. In Schultz and Klement 1963, pp. 539-56.
- Davis, J. J., R. W. Coopey, D. G. Watson, C. C. Palmiter, and C. L. Cooper. 1952. The radioactivity and ecology of aquatic organisms of the Columbia River. In *Hanford Works 1952*, pp. 19-29.
- Denham, D. H. and D. A. Waite. 1982. Action guides and countermeasures. In *CRC handbook of environmental radiation*, ed. A. W. Klement, pp. 187-204. Boca Raton, Fla: CRC Press, Inc.

- Department of Energy. 1977. *Formerly utilized MED/AEC sites, remedial action program. Radiological survey of the Hooker Chemical Company, Niagara Falls, N.Y.* DOE/EV-0005/2. Washington, D.C.
- Department of Energy. 1978. *Formerly utilized MED/AEC sites, remedial action program. Radiological survey of the former VITRO rare metals plant, Canonsburg, Pennsylvania.* DOE/EV-0005/3. Washington, D.C.
- Department of Energy. 1979a. *Formerly utilized MED/AEC sites, remedial action program. Radiological survey of the former Horizons, Inc., Metal Handling Facility, Cleveland, Ohio.* DOE/EV-0005/10. Washington, D.C.
- Department of Energy. 1979b. *Formerly utilized MED/AEC sites, remedial action program. Radiological survey of the Seneca Army Depot, Romulus, New York.* DOE/EV-0005/11. Washington, D.C.
- Department of Energy. 1981. *TRU waste management program, national strategy document.* DOE/AL-TRU-8002. Washington, D.C.
- Dickson, C. R. and G. E. Start. 1970. *Plutonium releases to the environment at Rocky Flats.* Memorandum to the files. ESSA Research Laboratories, February 4, 1970.
- DOE. See Department of Energy.
- Donaldson, L. 1979. Taped interview at the Univ. of Wash., May 1979.
- Donaldson, L. R. and R. F. Foster. 1957. Effects of radiation on aquatic organisms. Chapter 10 in NAS-NRC 1957, pp. 96-102.
- Dreyer, N. A., J. E. Loughlin, F. H. Fahey, and N. H. Harley. 1982. The feasibility of epidemiologic studies of cancer in residents near the Rocky Flats Plant. *Health Phys.* 42:65-68.
- Dunaway, P. B. and S. V. Kaye. 1963. Effects of ionizing radiation on mammal populations on the White Oak Lake Bed. In Schultz and Klément, pp. 333-38.
- Dunster, H. J. 1958. The disposal of radioactive liquid wastes into coastal waters. In *Proceedings of the 2d international conference on peaceful uses of atomic energy*, ser. 12, pp. 566-82. Held in Geneva, September 1-13, 1958. New York: United Nations.
- Dunster, H. J., H. Howells and W. L. Templeton. 1958. District surveys following the Windscale incident, October 1957. In *Proceedings of the 2d international conference on peaceful uses of atomic energy*, vol. 18, pp. 296-308. New York: United Nations. Also in *Progress in nuclear energy*, vol. 1, Health Physics, pp. 458-85. New York-London: Pergamon Press.
- Eisenbud, M. 1963. *Environmental radioactivity*. New York: McGraw Hill.
- Eisenbud, M. 1973. *Environmental radioactivity*, 2d ed. New York-London: Academic Press.
- Eisenbud, M. 1975. Early occupational exposure experience with uranium processing. In ERDA 1975, pp. 9-24.
- Elwood, J. W. 1971. Ecological aspects of tritium behavior in the environment. In *Consequences of effluent release*, ed. K. E. Cowser. *Nuclear Safety* 12:326-37.
- Emery, R. M. and D. C. Klopfer. 1976. The distribution of transuranic elements in a freshwater pond system. Chapter 13 in Miller and Stannard 1976, pp. 269-85.
- Emery, R. M., D. C. Klopfer, and M. C. McShane. 1980. The migration of plutonium from a freshwater ecosystem at Hanford. In Hanson 1980, pp. 625-43.
- Emery, R. M. and M. C. McShane. 1980. Nuclear waste ponds and streams on the Hanford Site: An ecological search for radiation effects. *Health Phys.* 38:787-809.
- Energy Research and Development Administration. 1975. *Conference on occupational health experience with uranium*, ERDA-93. Held in Arlington, Va., April 28-30, 1975. Washington, D.C.
- Environmental Protection Agency. 1977. *Radiological quality of the environment in the United States, 1977.* EPA 520/1-77-009. Washington, D.C.
- Environmental Protection Agency. 1981. *Environmental standards and radiation protection guidance for management and disposal of spent fuel, high-level and transuranic radioactive waste.* Working document no. 19, 40 CFR 191. Washington, D.C.
- EPA. See Environmental Protection Agency.
- ERDA. See Energy Research and Development Administration.

- Fabrikant, J. I. 1981. Health effects of the nuclear accident at Three Mile Island. Guest editorial, *Health Phys.* 40:151-61.
- Fadeley Cunningham, R. 1965. Oregon malignancy pattern physiographically related to Hanford, Washington, radioisotope storage. *J. Environ. Health* 27:883-97.
- Fair, D. R. R. and A. S. McLean. 1956. The radioactive survey of the area surrounding an atomic energy factory. In *Proceedings of the international conference on the peaceful uses of atomic energy*, vol. 13, pp. 329-32. Held in Geneva, August 8-20, 1955. New York: United Nations.
- Feldman, I. 1976. The colloidal nature of radionuclides in seawater. Chapter 9 in Miller and Stannard 1976, pp. 183-90.
- Feldt, W. 1971. Research on the maximum radioactive burden of some German rivers. In IAEA 1971, pp. 495-506.
- Fickeisen, D. H. and B. E. Vaughan. 1984. *Behavior of complex mixtures in aquatic environments*. PNL-5135. Richland, Wash.: Pacific Northwest Laboratory.
- Field, E. H., D. A. Zegers, and G. L. Steucek. 1981. Iodine-131 in thyroids of the meadow vole (*Microtus pennsylvanicus*) in the vicinity of the Three Mile Island nuclear generating plant. *Health Phys.* 41:297-301.
- Fitzgerald, J. J., H. Hurwitz, Jr., and L. Tanks. 1954. *Method for evaluating radiation hazards from a nuclear incident*. KAPL-1045. Schenectady, N.Y.: Knolls Atomic Power Laboratory.
- Folsom, T. R. and A. C. Vine. 1957. On the tagging of water masses for the study of physical processes in the oceans. Chapter 12 in NAS-NRC 1957, pp. 121-32.
- Foreman, H., ed. 1970. *Nuclear power and the public*. Minneapolis, Minn.: Univ. of Minn. Press.
- Foster, R. F. 1952. Biological problems associated with the discharge of pile effluent into the Columbia River. In *Hanford Works 1952*, pp. 11-13.
- Foster, R. F. 1963. *Environmental behavior of chromium and neptunium*. In Schultz and Klement 1963, pp. 569-76.
- Foster, R. F. 1972. The history of Hanford and its contribution of radionuclides to the Columbia River. Chapter 1 in Pruter and Alverson 1972, pp. 3-18.
- Foster, R. F. 1979. Taped interview, June 11, 1979, in Richland, Wash.
- Foster, R. F. and J. J. Davis. 1956. The accumulation of radioactive substances in aquatic forms. In *Proceedings of the international conference on the peaceful uses of atomic energy*, vol. 13, pp. 364-67. Held in Geneva, August 8-20, 1955. New York: United Nations.
- Fowler, E. B., R. W. Henderson, and M. F. Milligan. 1971. *Proceedings of environmental plutonium symposium*, LA-4756. Held in Los Alamos, August 1971. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- French, N. R. (undated). Chronic low-level gamma irradiation in a desert ecosystem for five years. In *Actes du symposium international de radioécologie*, vol. 2, pp. 1151-65. Centre d'Etudes Nucléaires de Cadarache, France.
- French, N. R. 1964. *Description of a study of ecological effects on a desert from chronic exposure to low-level ionizing radiation*. UCLA-12-532. Washington, D.C.: U.S. Atomic Energy Commission.
- French, N. R. 1965. Radiation and animal populations: Problems, progress and projections. *Health Phys.* 11:1557-68.
- French, N. R. 1969. Radiation sensitivity of rodent species. *Nature* 222:1003-4.
- Gofman, J. W. 1981. Tritium: A radionuclide of public concern. Chapter 12, section E in *Radiation and human health*, pp. 425-28. San Francisco: Sierra Club Books.
- Hakanson, T. E. and K. V. Bostick. 1976. Cesium-137 and plutonium in liquid waste discharge areas at Los Alamos. In Cushing 1976, pp. 40-48.
- Hammond, S. E. 1971. Industrial-type operations as a source of environmental plutonium. In Fowler, Henderson, and Milligan 1971, pp. 25-42.
- Hanford Works. 1952. *Biology research—Annual Report 1951* by the staff of the Biology Section [H. A. Kornberg, manager] of the Radiological Sciences Department [H. M. Parker, manager]. HW-25021, declassified April 15, 1952. Richland, Wash.

- Hanson, W. C. 1963. Iodine in the environment. In Schultz and Klement 1963, pp. 581-601.
- Hanson, W. C., ed. 1980. *Transuranic elements in the environment*, DOE/TIC-22800. A summary of environmental research on transuranium radionuclides funded by the U.S. Department of Energy through calendar year 1979. Springfield, Va.: National Technical Information Service.
- Hanson, W. C. and R. L. Browning. 1952. Biological monitoring. In *Hanford Works 1952*, pp. 202-03.
- Hanson, W. C. and H. A. Kornberg. 1956. Radioactivity of terrestrial animals near an atomic energy site. In *Proceedings of the international conference on the peaceful uses of atomic energy*, vol. 13, pp. 385-88. Held in Geneva, August 8-20, 1955. New York: United Nations.
- Hanson, W. C. and F. R. Miera, Jr. 1977. Long-term ecological effects of exposure to uranium. In *Biomedical and Environmental Research Program of the LASL Health Division*, LA-6898-PR, pp. 77-80. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Hanson, W. C. and F. R. Miera, Jr. 1978. Further studies of long-term ecological effects of exposure to uranium. In *Biomedical and Environmental Research Program of the LASL Health Division*, LA-7162. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Harrison, F. L., J. J. Koranda, and J. S. Tucker. 1973. Tritiation of aquatic animals in an experimental marine pool. In Moghissi and Carter 1973, pp. 363-78.
- Harrison, F. L., K. M. Wong, and R. E. Heft. 1976a. *Interactions of radionuclides in water, particulates, and oysters in the discharge canal of a nuclear power plant*. UCRL-51974. Livermore, Calif.: Lawrence Livermore Laboratory.
- Harrison, F. L., K. M. Wong, and R. E. Heft. 1976b. Role of solubles and particulates in radionuclide accumulation in the oyster, *Crassostrea gigas* in the discharge canal of a nuclear power plant. In Cushing 1976, pp. 9-20.
- Hart, J. C., ed. 1974. Population doses from the nuclear industry to 2000 A.D. By editorial staff of *Nuclear Safety*. In *Consequences of effluent release*. *Nucl. Saf.* 15:56-66.
- HASL. See Health and Safety Laboratory.
- Health and Safety Laboratory. 1959. *Symposium on occupational health experience and practices in the uranium industry*, HASL-58. Held in New York City, October 15-17, 1958. New York: Energy Research and Development Administration.
- Health and Safety Laboratory. 1975. *Health and Safety Laboratory environmental quarterly*, HASL-291, pp. 1-3. New York: Energy Research and Development Administration.
- Healy, J. W. and J. J. Fuquay. 1959. Wind pick up of radioactive particles from the ground. In *Progress in nuclear energy*, ser. 12, Health Physics, pp. 417-36. New York-London: Pergamon Press.
- Healy, J. W., B. V. Andersen, H. V. Clukey, and J. K. Soldat. 1959. Radiation exposure to people in the environs of a major production atomic energy plant. In *Progress in nuclear energy*, ser. 12, Health Physics, pp. 439-57. New York-London: Pergamon Press.
- Heer, J. E., Jr. and D. J. Hagerty. 1977. *Environmental assessments and statements*. New York: Van Nostrand-Reinhold.
- Herde, K. 1978. Letter to the author with enclosures, dated October 30, 1978.
- Hines, N. O. 1962. The laboratory. Chapter 1 in *Proving ground, an account of the radiobiological studies in the Pacific, 1946-1961*, pp. 3-19. Seattle: Univ. of Wash. Press. [Note: Although the book is officially labeled as an interim report because many long-term results were yet to come in, there is no comparable compilation of the work of this important laboratory.]
- Hoenes, G. R. and J. K. Soldat. 1977. *Age-specific radiation dose commitment factors for a one-year chronic intake*. NUREG-0172. Springfield, Va.: National Technical Information Service.
- Holland, J. Z. 1956. Radiation from clouds of reactor debris. In *Proceedings of the international conference on the peaceful uses of atomic energy*, vol. 13, pp. 110-18. Held in Geneva, August 8-20, 1955. New York: United Nations.
- Holm, E. 1977. *Plutonium isotopes in the environment—A radioecological study*. Univ. of Lund, Sweden: Department of Radiation Physics.

- Honstead, J. F. 1969. *Recreational use of the Columbia River—Evaluation of environmental exposure*. BNWL-CC-2299. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Honstead, J. F. 1970. Quantitative evaluation of environmental factors affecting population exposure near Hanford. In Voillequé and Baldwin 1970, vol. 2, pp. 266-77.
- Howells, H. 1966. Discharges of low-activity, radioactive effluent from the Windscale Works into the Irish Sea. In *Disposal of radioactive wastes into seas, oceans and surface waters*. Vienna: International Atomic Energy Agency.
- Howells, H. 1969. A review of some past emergencies with consideration of their public health implications. In IAEA 1969, pp. 521-27.
- Hungate, F. P., ed. 1965. Radiation and terrestrial ecosystems. Proceedings of the 4th annual Hanford biology symposium held in Richland, Wash., May 3-5, 1965. *Health Phys.* 11:1255-1675.
- IAEA. See International Atomic Energy Agency.
- ICRP. See International Commission on Radiological Protection.
- International Atomic Energy Agency. 1960. *Disposal of radioactive waste*. Proceedings of a conference held in Monaco, November 1959. STI/PUB/18. Vienna: International Atomic Energy Agency.
- International Atomic Energy Agency. 1963. *Disposal of radioactive wastes into fresh water*. Report of an ad hoc panel. Safety series no. 10-STI/PUB/44. Vienna: International Atomic Energy Agency.
- International Atomic Energy Agency. 1966a. *Disposal of radioactive wastes into seas, oceans and surface waters*. Proceedings of a conference held in Vienna, May 1966. STI/PUB/126. Vienna: International Atomic Energy Agency.
- International Atomic Energy Agency. 1966b. *Practices in the treatment of low- and intermediate-level radioactive wastes*. Proceedings of a symposium held in Vienna, December 6-10, 1965. STI/PUB/116. Vienna: International Atomic Energy Agency.
- International Atomic Energy Agency. 1967. *Disposal of radioactive wastes into the ground*. Proceedings of a symposium held in Vienna, May 29-June, 1967. STI/PUB/156. Vienna: International Atomic Energy Agency.
- International Atomic Energy Agency. 1968. *Management of radioactive wastes at nuclear power plants*. Safety series no. 28, STI/PUB/208. Vienna: International Atomic Energy Agency.
- International Atomic Energy Agency. 1969. *Environmental contamination by radioactive materials*. Proceedings of a symposium held in Vienna, March 24-28, 1969. STI/PUB/226. Vienna: International Atomic Energy Agency.
- International Atomic Energy Agency. 1971. *Environmental aspects of nuclear power stations*. Proceedings of a symposium held in New York, August 10-14, 1970. STI/PUB/261. Vienna: International Atomic Energy Agency.
- International Atomic Energy Agency. 1974. *Population dose evaluation and standards for man and his environment*. Proceedings of a seminar held in Portorož, Yugoslavia, May 28-24, 1974. STI/PUB/375. Vienna: International Atomic Energy Agency.
- International Atomic Energy Agency. 1975. *Impacts of nuclear releases into the aquatic environment*. Proceedings of a symposium held at Otaniemi, Finland, June 30-July 4, 1975. STI/PUB/406. Vienna: International Atomic Energy Agency.
- International Atomic Energy Agency. 1976a. *Effects of ionizing radiation on aquatic organisms and ecosystems*. Technical report series no. 172. Vienna: International Atomic Energy Agency.
- International Atomic Energy Agency. 1976b. *Transuranium nuclides in the environment*. Proceedings of a symposium held in San Francisco, November 17-21, 1975. Vienna: International Atomic Energy Agency.
- International Atomic Energy Agency. 1979a. *Behavior of tritium in the environment*. Proceedings of a symposium held in San Francisco, October 16-20, 1978. STI/PUB/498. Vienna: International Atomic Energy Agency.
- International Atomic Energy Agency. 1979b. *Biological implications of radionuclides released from nuclear industries*. Proceedings of a symposium held in Vienna, March 26-30, 1979, STI/PUB/522. [Two volumes.] Vienna: International Atomic Energy Agency.

- International Commission on Radiological Protection. 1965. *Principles of environmental monitoring related to the handling of radioactive materials*. Report of Committee 4, publ. 7. Oxford-London-New York: Pergamon Press. (Adopted September 13, 1965.)
- International Commission on Radiological Protection. 1979. *Limits for intakes of radionuclides by workers*. Publ. 30, pt. 1. Annals of the ICRP 2, no. 3/4. Oxford-New York-Frankfurt: Pergamon Press.
- Jinks, S. M. and M. E. Wrenn. 1976. Radiocesium transport in the Hudson River Estuary. Presented at the 8th Rochester international conference on environmental toxicity. Chapter 11 in Miller and Stannard 1976, pp. 207-27.
- Johnson, C. J. 1979. *An epidemiological evaluation of the health effects in a general population residing in an area contaminated with plutonium: A preliminary report*. Proceedings of the 6th international congress of radiation research held in Tokyo, May 13-19, 1979.
- Jordan, C. F., J. J. Koranda, J. R. Kline, and J. R. Martin. 1970. Tritium movement in a tropical ecosystem. *Bioscience* 20:807-12.
- Kaye, S. V. and P. B. Dunaway. 1963. Estimation of dose rate and equilibrium state for bioaccumulation of radionuclides by mammals. In Schultz and Klement 1963, pp. 107-111.
- Kirchmann, R., G. Köch, V. Adam, and J. Van Den Hoek. 1973. Studies on the food chain contamination by tritium. In Moghissi and Carter 1973, pp. 341-48.
- Klement, A. W., Jr., and V. Schultz. 1980. *Freshwater and technical ecology. A selected bibliography*. Stroudsburg, Pa.: Dowden, Hutchinson, and Ross, Inc.
- Klement, A. W., Jr. et al. 1972. *Estimates of ionizing radiation doses in the United States, 1960-2000*. ORP/CSD-72-1. Washington, D.C.: U.S. Environmental Protection Agency.
- Koranda, J. J. and J. R. Martin. 1973. The movement of tritium in ecological systems. In Moghissi and Carter 1973, pp. 430-55.
- Kornberg, H. A. and J. J. Davis. 1966. Food chains in fresh water. Chapter 18 in *Radioactivity and human diet*, ed. R. S. Russell, pp. 385-418. New York-Oxford-London: Pergamon Press.
- Krey, P. W. 1974. Plutonium-239 contamination in the Denver area. *Health Phys.* 26:117-20.
- Krey, P. W. 1976. Remote plutonium contamination and total inventories from Rocky Flats. *Health Phys.* 30:209-14.
- Krey, P. W. 1979. Letter to Carl J. Johnson, Jefferson County (Colo.) Health Department, April 16, 1979.
- Krey, P. W. and E. P. Hardy. 1970. *Plutonium in soil around the Rocky Flats Plant*. HASL-235. New York: Environmental Research and Development Administration, Health and Safety Laboratory.
- Krumholz, L. A., E. D. Goldberg, and H. Boroughs. 1957. Ecological factors involved in the uptake, accumulation, and loss of radionuclides by aquatic organisms. Chapter 7 in NAS-NRC 1957, pp. 69-79.
- Kuper, J. B. H. and F. P. Cowan. 1959. Exposure criteria for estimating the consequences of a catastrophe in a nuclear plant. In *Proceedings of the 2d international conference on the peaceful uses of atomic energy*, vol. 18, pp. 319-24. Geneva: United Nations. Also in *Progress in nuclear energy*, ser. 12, vol. 1, Health Physics, pp. 60-70. Oxford-London-New York: Pergamon Press.
- Langham, W. H. 1971. Plutonium distribution as a problem in environmental science. In Fowler, Henderson, and Milligan 1971, pp. 3-19.
- Larsen, R. P. and R. D. Oldham. 1978. Plutonium in drinking water: Effects of chlorination on its maximum permissible concentration. *Science* 201:1008-9.
- Larson, K., A. Welander, and K. Bonham. 1979. Taped joint interview, Univ. of Wash., June 1, 1979.
- LASL. See Los Alamos Scientific Laboratory.
- Lentsch, J. W., M. E. Wrenn, T. J. Kneip, and M. Eisenbud. 1970. Manmade radionuclides in the Hudson River Estuary. In Voillequé and Baldwin 1970, vol. 2, pp. 499-528.

- Léonard, B. P., Jr. 1959. Hazards associated with fission product release. In *Proceedings of the 2d international conference on the peaceful uses of atomic energy*, vol. 11, pp. 157-70. Geneva: United Nations. Also in *Progress in nuclear energy*, ser. 12, vol. 1, pp. 369-98. Oxford-London-New York: Pergamon Press.
- Marley, W. G. and T. M. Fry. 1956. Radiological hazards from an escape of fission products and the implications in power reactor location. In *Proceedings of the international conference on the peaceful uses of atomic energy*, vol. 13, pp. 102-5. Held in Geneva, August 8-20, 1955. New York: United Nations.
- Marshall, E. 1983. The 'lost' mercury at Oak Ridge. *Science* 221:130-32.
- Martin, J. R. and J. J. Koranda. 1971. Distribution, residence time and inventory of tritium in Sedan Crater Ejecta. *Nucl. Technol.* 11:459-65.
- Martin, J. R., C. F. Jordan, J. J. Koranda, and J. R. Kline. 1970. Radioecological studies of tritium movement in a tropical rain forest. In *Symposium on engineering with nuclear explosives*, CONF-700101-P1, pp. 422-38. Held in Las Vegas, January 14-16, 1970. Springfield, Va.: National Technical Information Service.
- Miller, M. W. and J. N. Stannard, eds. 1976. *Environmental toxicity of aquatic radionuclides: Models and mechanisms*. Proceedings of the Rochester international conference on environmental toxicity. Ann Arbor, Mich.: Ann Arbor Science.
- Mitchell, N. T. 1969. Monitoring of the aquatic environment of the United Kingdom and its application to hazard assessment. In IAEA 1969, pp. 449-62.
- Moghissi, A. A. and M. W. Carter, eds. 1973. *Tritium*. Proceedings of a symposium held in Las Vegas, August 28-September 3, 1971. Las Vegas-Phoenix: Messenger Graphics.
- Moghissi, A. A., R. G. Patzer, and M. W. Carter. 1973. Biokinetics of environmental tritium. In Moghissi and Carter 1973, pp. 314-22.
- Morgan, K. Z. 1975. Suggested reduction of permissible exposure to plutonium and other transuranium elements. *Am. Ind. Hyg. Assoc. J.* 36:567-75.
- Myers, D. S. 1972. A plea for consistent lung burden criteria for insoluble alpha emitting isotopes. *Health Phys.* 22:905-9.
- NAS-NRC. See National Academy of Sciences-National Research Council.
- National Academy of Sciences-National Research Council. 1957. *The effects of atomic radiation on oceanography and fisheries*. Report of a NAS committee. NAS-NRC publ. 551. Washington, D.C.
- National Academy of Sciences-National Research Council. 1960. *The biological effects of atomic radiation*. Summary reports of committee on agriculture and food supplies, pp. 49-53; on disposal and dispersal of radioactive wastes, pp. 57-66; and on oceanography and fisheries, pp. 69-90. Washington, D.C.
- National Council on Radiation Protection and Measurements. 1979. *Tritium in the environment*, no. 62, p. 125. Washington, D.C.
- National Council on Radiation Protection and Measurements. 1982. *Preliminary evaluation of criteria for the disposal of transuranium contaminated waste*. Prepared by a task group of Scientific Committee-38 on waste disposal. Washington, D.C.
- NCRP. See National Council on Radiation Protection and Measurements.
- NEA. See Nuclear Energy Agency.
- Nelson, D. J. 1963. The strontium and calcium relationships in Clinch and Tennessee River mollusks. In Schultz and Klement 1963, pp. 203-11.
- Nelson, D. J., ed. 1971. *Radionuclides in ecosystems*, CONF-710501-P1 and P2. Proceedings of the 3d national symposium on radioecology held in Oak Ridge, May 10-12, 1971. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Nelson, D. J. and B. G. Blaylock. 1963. The preliminary investigation of salivary gland chromosomes of *Chironomus tentans* Fabr. from the Clinch River. In Schultz and Klement 1963, pp. 367-72.
- Nelson, D. J. and F. C. Evans, eds. 1969. *Symposium on radioecology*, CONF-670503. Proceedings of the 2d national symposium on radioecology held at Ann Arbor, Mich., May 15-17, 1967. Washington, D.C.: U.S. Atomic Energy Commission.
- Nelson, I. C. and R. F. Foster. 1965. Ringold Farms—A Hanford environmental study. *Health Phys.* 11:397-401.

- Nelson, V. A. 1972. Effects of strontium-90 + yttrium-90, zinc-65 and chromium-51 on the larvae of the Pacific Oyster *Crassostrea gigas*. In Pruter and Alverson 1972, pp. 819-32.
- Noshkin, V. E. 1972. Ecological aspects of plutonium dissemination in aquatic environments. *Health Phys.* 22:537-49.
- Noshkin, V. E., W. L. Robison and F. L. Harrison. 1976. *Radiological dose to man through the marine pathway from reactor operations at Humboldt Bay, California*. UCRL-52160. Livermore, Calif.: Lawrence Livermore Laboratory.
- Noshkin, V. E., J. L. Brunk, T. A. Jokela, and K. M. Wong. 1981. ^{238}Pu concentrations in the marine environment at San Clemente Island. *Health Phys.* 40:643-59.
- NRC. See Nuclear Regulatory Commission.
- Nuclear Energy Agency. 1980. *Radiological significance and management of tritium, carbon-14, krypton-85, iodine-129 arising from the nuclear fuel cycle*. Paris: Nuclear Energy Agency of the Organization for Economic Co-operation and Development.
- Nuclear Regulatory Commission. 1981. Licensing requirements for land disposal of radioactive waste. 10 CFR 61. Proposed regulations. *Federal Register* 46(142):38081.
- Nyhan, J. W., F. R. Miera, Jr., and R. J. Peters. 1976. The distribution of plutonium and cesium in alluvial soils of the Los Alamos environs. In Cushing, 1976, pp. 49-57. Stroudsburg, Pa.: Dowden, Hutchinson, and Ross, Inc.
- Oak Ridge National Laboratory. 1978. *Progress report*. Oak Ridge, Tenn.: Oak Ridge National Laboratory, Health and Safety Division.
- Oak Ridge National Laboratory. 1979. *Environmental sciences division publications*. Published April 1979, Oak Ridge, Tenn.
- Odum, E. P. 1956. Consideration of the total environment in power reactor waste disposal. In *Proceedings of the international conference on the peaceful uses of atomic energy*, vol. 13, pp. 350-53. Held in Geneva, August 8-20, 1955. New York: United Nations.
- Odum, E. P. 1971. Radiation ecology. Chapter in *Fundamentals of ecology*, 3d ed., pp. 451-67. Philadelphia, Pa.: W. B. Sanders.
- Olson, J. S. 1963. Analog computer models for movement of nuclides through ecosystems. In Schultz and Klement 1963, pp. 121-25.
- Ophel, I. L. 1963. The fate of radiostrontium in a freshwater community. In Schultz and Klement 1963, pp. 213-16.
- ORNL. See Oak Ridge National Laboratory.
- Paine, D. 1980. Plutonium in Rocky Flats freshwater systems. In Hanson 1980, pp. 644-58.
- Parker, H. M. 1956. Radiation exposure from environmental hazards. In *Proceedings of the international conference on the peaceful uses of atomic energy*, vol. 13, pp. 305-10. Held in Geneva, August 8-20, 1955. New York: United Nations.
- Parker, H. M. and J. W. Healy. 1956. Environmental effects of a major reactor disaster. In *Proceedings of the international conference on the peaceful uses of atomic energy*, vol. 13, pp. 106-9. Held in Geneva, August 8-20, 1955. New York: United Nations.
- Parker, the Hon. M. Justice. 1978. *The Windscale inquiry*. Presented to the Secretary of State for the Environment on January 26, 1978. Her Majesty's Stationary Office, U.K.
- Peterson, H. T., Jr., J. E. Martin, C. L. Weaver, and E. D. Haward. 1969. Environmental tritium contamination from increasing utilization of nuclear energy sources. In IAEA 1969, pp. 35-59.
- PHS. See Public Health Service.
- Poet, S. E. and E. A. Martell. 1972. Plutonium-239 and americium-241 contamination in the Denver area. *Health Phys.* 23:537-48.
- Poet, S. E. and E. A. Martell. 1974. Reply to "Plutonium-239 contamination in the Denver area" by P. W. Krey. *Health Phys.* 26:120-22.
- Polikarpov, G. G. 1966. *Radioecology of aquatic organisms. The accumulation and biological effect of radioactive substances*. Translated from the Russian by Scripta Technica, Ltd. English translation edited by V. Schultz and A. W. Klement, Jr. Amsterdam: North Holland Publishing Company; New York: Reinhold Book Division.
- Pruter, A. T. and D. L. Alverson, eds., 1972. *The Columbia River Estuary and adjacent ocean waters. Bioenvironmental studies*. Seattle-London: Univ. of Wash. Press.

- Public Health Service. 1966. *Routine surveillance of radioactivity around nuclear facilities*. Prepared by a subcommittee on environmental surveillance of the interlaboratory technical advisory committee of the Division of Radiological Health, U.S. Public Health Service (Environmental Health Sciences), Washington, D.C.
- Reinig, W. C., ed. 1970. *Environmental surveillance in the vicinity of nuclear facilities*. Springfield, Ill.: Charles C. Thomas.
- Revelle, R. and M. B. Schaefer. 1957. General considerations concerning the ocean as a receptacle for artificially radioactive materials. In NAS-NRC 1957, pp. 1-25.
- Robeck, G. C., C. Henderson, and R. C. Palange. 1954. *Water quality studies of the Columbia River*. Special report, U.S. Public Health Service, U.S. Department of Health, Education and Welfare. [Cited by Foster 1972.]
- Röhwer, P. S., M. J. Kelly, and R. S. Booth. 1973. Guidance for limiting environmental releases of tritium. In Moghissi and Carter 1973, pp. 422-30.
- Romney, E. M. and J. J. Davis. 1972. Ecological aspects of plutonium dissemination in terrestrial environments. *Health Phys.* 22:551-57.
- Rudolph, A. W., T. E. Carroll, and R. S. Davidson. 1971. *Plutonium and its effects in the environment—A selected literature survey*. Columbus, Ohio: Battelle Columbus Laboratories.
- Savannah River Ecology Laboratory. 1979. *Savannah River Ecology Laboratory*. Brochure prepared for the dedication program of the new building for the Laboratory, May 9, 1979, Aiken, S. C. [Kindly supplied by R. I. Nester.]
- Schaefer, M. B. 1957. Large-scale biological experiments using radioactive tracers. In NAS-NRC 1957, pp. 133-37.
- Schultz, V. and A. W. Klement, Jr., eds. 1963. *Radioecology*. Proceedings of the 1st national symposium on radioecology held at Colo. State Univ., Fort Collins, Colo., September 10-15, 1961. New York: Reinhold Publishing Corporation; Washington, D.C.: American Institute of Biological Sciences.
- Schultz, V. and F. W. Whicker. 1972. *Ecological aspects of the nuclear age: Selected readings in radiation ecology*. TID-25978. Springfield, Va.: National Technical Information Service.
- Seymour, A. H. 1971. Introduction in *Radioactivity and the marine environment*. Washington, D.C.: National Academy of Sciences-National Research Council.
- Seymour, A. 1979. Taped interview at the Univ. of Wash., June 1, 1979.
- Siek, R. D. and J. B. Baird, Jr. 1972. Uranium mill tailings problems in Grand Junction, Colo. *Health Physics Society Newsletter*, November 1972, pp. 12-21.
- Skauen, D. M. 1963. Tritium in ecology—A review. In Schultz and Klement 1963, pp. 603-9.
- Sobo, J. J. and P. H. Bedrosian, eds. 1963. *Studies on the fate of certain radionuclides in estuarine and other aquatic environments*. Public Health Service publication no. 999-R-3. Washington, D.C.: U.S. Department of Health, Education, and Welfare.
- Soldat, J. K. 1969. *Recommendations for evaluation of radiation doses potentially received by residents of the Hanford environs*. BNWL-CC-1998. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Soldat, J. K. 1979. Taped interview at Richland, Wash., June 7, 1979.
- Soldat, J. K. and J. F. Honstead. 1968. *Dietary levels for Tri-City elementary school children*. BNWL-CC-1565. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- SREL. See Savannah River Ecology Laboratory.
- Stannard, J. N. 1973a. Plutonium in the environment. Chapter 15 in *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh, pp. 669-88. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.
- Stannard, J. N. 1973b. Toxicology of radionuclides. *Annu. Rev. Pharmacol.* 13:325-57.
- Strand, J. A., W. L. Templeton, and P. A. Olson. 1976. Fixation and long-term accumulation of tritium from tritiated water in an experimental aquatic environment. In *Radiation effects and tritium technology for fusion reactors*, CONF-750989, vol. 3, pp. III-77 to III-95. Proceedings of a conference held in Gatlinburg, Tenn., October 1-3, 1975. Springfield, Va.: National Technical Information Service.

- Strand, J. A., W. L. Templeton, and E. G. Tangen. 1971. Accumulation and retention of tritium (tritiated water) in embryonic and larval fish, and radiation effect. In Nelson 1971, vol. 1, pp. 445-51.
- Strand, J. A. and R. C. Thompson. 1976. *Biological effects of tritium releases from fusion power plants*. BNWL-2022. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Strand, J. A., M. P. Fujihara, R. D. Burnett, and T. M. Poston. 1977. Suppression of the immune response in rainbow trout, *Salmo gairdneri*, sublethally exposed to tritiated water during embryogenesis. *J. Fish Res. Board Can.* 34(9):1293-1304.
- Strand, J. A., M. P. Fujihara, T. M. Poston, and C. S. Abernethy. 1982. Permanence of suppression of the primary immune response in rainbow trout, *Salmo gairdneri*, sublethally exposed to tritiated water during embryogenesis. *Radiat. Res.* 91:533-41.
- Strand, J. A., M. P. Fujihara, W. L. Templeton, and E. G. Tangen. 1973. Suppression of *Chondrococcus columnaris* immune response in rainbow trout sublethally exposed to tritiated water during embryogenesis. In *Radioactive contamination of the marine environment*, pp. 543-49. Proceedings of a symposium held in Seattle, Wash., July 10-14, 1972. Vienna: International Atomic Energy Agency.
- Struxness, E. G., P. H. Carrigan, Jr., M. A. Churchill, K. E. Cowser, R. J. Morton, D. J. Nelson, and F. L. Parker. 1967. *Comprehensive report of the Clinch River study*. ORNL-4035. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Templeton, W. L. 1976. Effects of radiation on aquatic populations. Chapter 14 in Miller and Stannard, pp. 287-301.
- Thompson, R. C. and W. J. Bair, eds. 1972. The biological implications of the transuranium elements. Proceedings of the 11th annual Hanford biology symposium held in Richland, Wash., September 27-29, 1971. *Health Phys.* 22:533-954.
- Till, J. E. 1976. A comparison of environmentally released recycled uranium-233 HTGR fuel and LMFBR plutonium fuel. In Cushing 1976, pp. 58-64.
- Tsivoglou, E. C. 1959. Radioactive waste disposal to surface waters. In *Industrial radioactive waste disposal*. Hearings before the Joint Committee on Atomic Energy, Congress of the United States, January-February 1959.
- Tsivoglou, E. C., A. F. Bartsch, D. E. Rushing, and D. A. Holaday. 1958. Effects of uranium ore refining wastes on receiving waters. *Sewage and Ind. Wastes* 30:1012-1027.
- Tsivoglou, E. C., S. D. Shearer, Jr., J. O. Jones, and D. A. Clark. 1960. Estimating human radiation exposure on the Animas River. *J. Am. Water Works Assoc.* 52:1271-90.
- USAEC. See Atomic Energy Commission.
- USPHS. See Public Health Service.
- Voillequé, P. G. and B. R. Baldwin, eds. 1970. *Health physics aspects of nuclear facility siting*. Proceedings of the Health Physics Society 5th annual midyear topical symposium held in Idaho Falls, November 3-6, 1970. [Three volumes.] Idaho Falls: Eastern Idaho Farmer Printing Company.
- Watters, R. L. 1980. Foreword in Hanson 1980, pp. iii-v.
- Watters, R. L., D. N. Edgington, T. E. Hakonson, W. C. Hanson, M. H. Smith, F. W. Whicker, and R. E. Wildung. 1980. Synthesis of the research literature. In Hanson 1980, pp. 1-44.
- Wehner, G. 1979. Discharges of tritium to the environment from unrestricted use of consumer products containing this radionuclide. In *Behavior of tritium in the environment*, pp. 79-91. Vienna: International Atomic Energy Agency.
- Weik, M. H. 1969. *Hearings before the Joint Committee on Atomic Energy, 9th Congress of the United States, part I*, p. 104-5.
- Whicker, F. W. and V. Schultz. 1982. *Radioecology: Nuclear energy and the environment*, 2 vol. Boca Raton, Fla: CRC Press, Inc.
- Witherspoon, J. P., Jr. 1963. Cycling of cesium-134 in white oak trees on sites of contrasting soil type and moisture. I. 1960 growing season. In Schultz and Klement 1963, pp. 127-32.
- Woodwell, G. M., ed. 1965. *Ecological effects of nuclear war*. Proceedings of a symposium held in Amherst, Mass., August 1963. BNL-917 (C-43), p. 72. Upton, N.Y.: Brookhaven National Laboratory.

- Wrenn, M. E. and S. M. Jinks. 1976. The dosimetric implications of releases to the aquatic environment from the nuclear power industry. Chapter 12 in Miller and Stannard, pp. 229-65.
- Wrenn, W. E., S. M. Jinks, N. Cohen, and L. M. Hairr. 1974. ^{137}Cs and ^{134}Cs distribution in sediment, water, and biota of the Lower Hudson River and their dosimetric implications for man. In *Proceedings of the 3d international congress of the International Radiation Protection Association*, ed. W. S. Snyder, CONF-730907-P1, pp. 279-84. Held in Washington, D.C., September 9-14, 1973. Oak Ridge, Tenn.: Technical Information Center.

OUTLINE

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Capsule Chronology

- July 1945** Trinity Test—Alamogordo, New Mexico. Possibility of fallout contamination considered and measurements made. Monitoring of area and local inhabitants continues for several months (UCLA and Berkeley).^(a) Cattle receive beta burns, and some go to Oak Ridge after a few months.
- August 1945** Photographic film at Eastman Kodak Company fogged from contamination of packaging materials that incorporated fallout from Trinity. Not published until 1949 (Webb, Eastman Kodak Co. at Rochester).
Hiroshima and Nagasaki bombs: Fallout plays only a small role because bursts were high. However, contamination reported many years later.
- June–July 1946** Operation Crossroads at Bikini. Underwater shot (Test Baker) provides graphic demonstration of possible dimensions of fallout contamination of ships, personnel, and environment. Work continues for several months. Potential appreciated for contamination of marine biota, including organisms attached to the hulls of ships.
- 1947** Resurvey of Bikini begins (Donaldson et al., University of Washington; U.S. Navy; Hopkins Marine Station; Scripps Institution of Oceanography; Oak Ridge; others).
Idea of Pacific Proving Grounds gains.
UCLA Atomic Energy Project organized. Takes active role in tests and fallout measurements for decades thereafter (Warren, Larson, Romney et al.).
Results of animal exposures at Operation Crossroads published (Tullis and Warren, Harvard; Navy).
- 1948** Sandstone Tests in Enewetak area. Follow-up shows tumors in plants.
Further follow-up of Bikini contamination and effects.
Follow-up of contamination at Trinity Site (Bellamy, Larson et al., UCLA) started in summer 1947. Area of fallout found to be much larger than 1945 measurements indicated.
- 1949** Fogging of photographic film at Eastman Kodak from Trinity Fallout published.
President Truman announces that Russia has exploded a nuclear device.
- 1950** Nevada site designated to meet needs for test site in continental United States. Site for 582 announced shots, plus many unannounced. About 100 of the total were in the atmosphere.
- 1950s** Continuing studies of marine and terrestrial biota at Pacific Proving Grounds. Continued intermittently through present.
- 1951** Greenhouse test series in Pacific; animals exposed.
First tests at Nevada Test Site (NTS)—Operation Ranger.
Radioactive snows detected in several cities.
More resurvey of Trinity site (Larson et al., UCLA).
Contamination of biota on NTS first described (UCLA).

(a) For abbreviations and acronyms, see Appendix D.

- 1951 Sunshine Project and unit developed by Willard Libby.
- 1952 Ivy series in the Pacific. Mike shot, one of the first thermonuclear devices raises potential for contamination from fallout by a large factor.
Tumbler-Snapper series at NTS.
- 1953 Airborne radioactive materials from three NTS shots (Snapper) characterized (Olafson et al., UCLA)
Eisenbud spearheads fallout collection network using sticky paper and air sampling. Publishes a summary of findings.
Sheep exposures occur in Nevada-Utah; deaths blamed on NTS tests.
Comparative study of Hanford and Utah range sheep (Bustad et al., Hanford).
Permanent laboratory for biology established in the Pacific islands. Used especially by University of Washington and AEC New York Operations office people.
First reports of PHS participation in offsite monitoring at NTS. Also PHS air sampling network established.
Upshot-Knothole series at NTS.
- 1954 Castle series in Pacific. Shot Bravo makes fallout a worldwide concern. Contamination of Marshall Islands and the Marshallese and of a Japanese fishing boat triggers enormous responses. These include over three decades of study and medical care of the exposed Marshall Islanders (Conard, Cronkite, et al., Brookhaven; also personnel from NRDL; Naval Medical Center; Walter Reed Hospital; others).
Lucky Dragon arrives at home port (March 17) with twenty-two sick fishermen. Causes uproar in Japan, with much concern for contamination of seafood as well as health of fishermen. Much good scientific detective work by Japanese on what occurred. High-level conferences for balance of year.
The Lucky Dragon and Marshallese incidents constitute a watershed in general attitudes toward the potentials of fallout.
Iodine first reported in cattle thyroids at market in the United States. Report of high levels of radioactivity in rain at Troy, New York.
- 1954-1956 Expeditions mounted to check seawater and seafood contamination in Pacific, particularly the western Pacific.
- 1955 Congressional hearings on fallout. Documentation of global fallout levels.
Teapot series at NTS.
Radioactivity measurements made part of Water Quality Control network.
- Mid-1950s Role of food chains in transfer of fallout radionuclides becomes very evident, especially for iodine and strontium.
- 1956 Redwing series in the Pacific.
Sunshine Project data made available by Libby publications; followed by others.
Lawsuit filed by sheep ranchers.

- 1956** Reviews published of medical care of Marshall Islanders.
 NAS-NRC reports on Biological Effects of Atomic Radiation (BEAR).
 British Medical Research Council report on same subject. Both concentrate on fallout. NAS-NRC series continues in later years.
 Strontium content of human bone and of stillborns, calf and sheep bones given by Libby.
 Los Alamos does survey of cesium in milk.
- 1957** More Congressional hearings on nature of fallout; standards and the "worry dose" considered.
 Unclassified report documents events of Shot Bravo (Dunning, AEC). Eisenbud and Libby present series on global fallout.
 Safety criteria explained.
 Repatriated populations on some of the Marshall Islands begin to show mounting body contents of radioactivity, apparently from food.
 Plumbbob series at NTS.
 Comar's work on thyroid contamination from fallout.
 USPHS report on iodine in thyroids of small animals (Wolff).
 Reports on fallout in man from Lamont group (Kulp, Columbia University).
- 1958** Hardtack, Phase I series at Pacific Proving Grounds, Phase II at NTS.
 Publication of estimates of radiation exposures from Nevada Test Site (Dunning, AEC).
 Los Alamos summarizes hazards of worldwide fallout (Langham and Anderson).
 Fallout discussions become more and more wide-ranging and strident.
 Further oceanic surveys, as part of Operation Hardtack, Phase I.
 United Nations Scientific Committee on Effects of Atomic Radiation (UNSCEAR) begins periodic review of all radiation sources, but concentrates on fallout radionuclides.
 Hazard from ^{14}C evaluated (Totter et al., AEC; Pauling, Cal. Tech.).
 Summaries of cesium in the biosphere by Langham and Anderson (Los Alamos).
 Moratorium on nuclear testing declared in November; ends September 1961.
- 1959** Lawrence's book on Trinity.
 NTS changes to underground testing; a few release radioactivity offsite.
 Consumers Union samples teenagers' diets.
- 1960** Summary characterization of fallout at NTS after a decade of testing (Larson and Neel, UCLA).
- 1960 et seq.** Federal Radiation Council (FRC) sets out basic radiation protection guides for population as well as workers, also protective action guides for use when intake period is short. Much attention to fallout problems, especially strontium and iodine. Reports of NAS-NRC advisory committees to FRC.

- 1960 et seq.** Biota surveys continue at Pacific atolls: Lawrence Livermore Laboratory (LLL) added to those named earlier.
Special problems of arctic food chains uncovered (see chapter 15).
Tri-City Study under way. Analyses of food in New York, Chicago, and San Francisco for fallout radionuclides.
- 1961** Bibliography of world's literature on radioactive fallout (Bost et al., AEC).
- 1961-1967** USPHS institutional diet sampling program for fallout radionuclides.
- 1961-1969** FDA sampling of whole diet for fallout radionuclides.
- 1962** More Congressional hearings on fallout problems.
Utah studies of iodine in fallout, milk, and people reach most active stage (Pendleton, Lloyd, Mays).
Offsite monitoring by PHS described in detail.
- 1963-1967** Connecticut State Department of Health sampling of representative diet of 18-year olds.
- 1963** Congressional hearings on Fallout, Radiation Standards and Counter-measures. Includes many estimates of radiation dose from global and local fallout.
The Knapp study on iodine in milk. More in hearings.
Further measurements of seafood contamination in the Pacific (Seymour, University of Washington; Lowman, Puerto Rico).
PHS plans study of thyroid and bone cancer, leukemia, and congenital malformations in southwestern Utah.
Limited Test Ban Treaty.
- 1964** Radioactive particles from fallout identified in lung tissue at autopsy (Wegst, Pelletier, and Whipple, University of Michigan).
PHS work on iodine in bovine thyroids.
FRC work on milk.
- 1964-1967** California State Department of Public Health sampling of house diets of hospitals for fallout radionuclides.
- 1965** Concepts of critical nuclides, critical pathways, and critical population groups suggested by ICRP (more in chapter 15).
PHS on ¹³¹I in children's thyroids.
Weiss's (PHS) paper on leukemia mortality in southwestern Utah.
- 1969** Thyroid nodules described in Marshall Islanders.
Series of reports by Sternglass linking infant mortality to fallout from nuclear weapons tests; summarized in his 1972 book. Causes much discussion and reanalysis of data over several years. Discussed by Tomkins and Brown (PHS) and Tamplin (LLL) in 1969.
FAO-IAEA-WHO Symposium on Environmental Contamination by Radioactive Materials. Emphasizes agricultural problems (see chapters 11 and 15).
Further work on arctic food chains (more in chapter 15).

- 1970** Baneberry event at NTS (venting of underground test shot). Much study locally and in Utah.
Nonproliferation treaty (March).
- 1971** Thyroid nodularity studied in school children of southwestern Utah (USPHS).
Report of Utah measurements subsequent to Baneberry event (Pendleton et al., University of Utah).
PHS (BRH) reports on search for thyroid abnormalities in "exposed" groups of Utah and Nevada versus "unexposed" group in Arizona. Studies begun in 1965.
- 1973** Report by Congress of Micronesia regarding contamination of Marshall Islands and the problems raised thereby.
Dose estimates from marine food chain at Enewetak (Robison, Koranda, LLL). Also evaluation of transuranics (several laboratories).
- 1974** Recommendations of AEC Task Group for Clean-up and Rehabilitation of Enewetak Atoll.
Publication of medical findings in Utah children.
Further PHS clinical studies in Utah and Nevada.
- 1975** Twenty-year report on Japanese fishermen (Kumatori).
- 1975-1976** Twenty-seven and twenty-eight year resurveys of Trinity site (Hakanson and Johnson et al., Los Alamos).
- 1975 et seq.** Much work using whole-body counters for measurement of body content of fallout radionuclides in general population.
- 1977** PHS Center for Disease Control finds "cluster" of leukemia cases in military participants in certain Nevada tests, e.g., Shot Smoky in Plumb-bob series. Called "Atomic Veterans." Defense Nuclear Agency begins review.
Dose commitment from fallout estimated by UNSCEAR. Also tritium inventory.
- 1978** Report of fallout contamination in inhabitants of Nagasaki suburb. Search for effects negative (Okajima, Nagasaki University, and ABCC).
Preventive and Emergency Action Guides for Population Exposure suggested by FDA.
- 1979** Lyon et al. propose that Nevada tests increased leukemia incidence in Utah. Use low- versus high-fallout counties over previous fifteen years. Much discussion follows. Problems in study pointed out by Land (National Cancer Institute) and Enstrom (UCLA).
Books prepared for Marshallese (Bair, Healy, Wachholz, et al.).
- 1980s** Offsite Radiation Exposure Review Project and Dose Assessment Advisory Group operated by DOE at Nevada Operations Office.
- 1980** Dietary radioactivity study of Marshall Islands indicates persistent contamination of local foods.
More on resettlement of Bikini people (Clusen, DOE).
Brookhaven begins to concentrate on reevaluating dosimetry, especially thyroid, in the Marshall Islands.

- 1980** Review of dose assessments from fallout from Nevada tests.
Comprehensive survey of comparative plutonium distribution at Trinity and Los Alamos (Hakanson and Nyhan).
Probability-of-occurrence approach to cancer risk from radiation exposure (Bond, Brookhaven).
- 1981** Radiation Exposure Compensation Act.
Feasibility study for epidemiologic investigation of populations of Nevada, Utah, and Arizona (Hoffman et al., BRH).
Approach to reconstruction of doses from fallout by measuring radioactivity of samples of bricks (Wrenn, University of Utah). Also suggests level of iodine be measured in old samples of thyroids removed in hospitals by determining long-lived iodine in paraffin blocks from pathology laboratories.
- 1982** New estimates of risk of resettling Bikini (Kohn and Dryer).
Scientists implicated in sheep cases.
- 1983** Announced that U.K. will study health effects of nuclear tests.
Report on soil sampling programs for residual ^{137}Cs and ^{239}Pu in parts of Nevada and Utah (Environmental Measurements Laboratory, DOE).
Book and Goldman publish overview of research during era of nuclear weapons testing (UC, Davis).
Final report on organ doses from radionuclide intake by Nuclear Test Personnel (Lee et al., Advanced Research and Applications, Inc.).
- 1984** Judge in Salt Lake City rules that fallout caused certain cases of cancer in exposed population.
More on childhood leukemia and fallout—negative results (Land et al., National Cancer Institute).
- 1986** Final appeal denied in sheep case.
- 1987** First volume of Hacker's review of radiation safety in the MED and at the tests published.

Chapter 12

New Dimension Number Three— Fallout From Nuclear Weapons Tests

Overview

This chapter reviews the biomedical aspects of the most pervasive and unsettling of the three "New Dimensions" brought upon the scientific and technical biocommunity by the advent of atomic energy. This, the latest of the new dimensions, involved both individual organisms and the entire biosphere. It spilled over into the sociopolitical arena and generated one of the most serious confrontations between science and society since the controversy over evolution, perhaps since the industrial revolution.

The chapter is organized chronologically within the major theatres of operation and technological problems. We begin with the very first nuclear weapons test, the Trinity shot at Alamogordo, New Mexico. We show that, contrary to much that has been said, the possibility of radioactive fallout was considered seriously. We consider the bombings of Hiroshima and Nagasaki, where fallout potential received relatively little attention, and then go to the first major test series, "Operation Crossroads," held at Bikini Atoll in the central Pacific Ocean. It is emphasized that this series, particularly the underwater shot, drove home the potential for serious, in fact lethal, contamination of a naval task force by radionuclides from fallout.

A major section is devoted to the tests at the Pacific Proving Grounds beginning with the resurvey of Bikini and progressing through the subsequent fission weapon shots to the thermonuclear weapon detonations. The "Bravo" shot of Operation Castle receives the attention it deserves as the first event to produce major contamination of a large area and to contaminate significant human populations. We follow the biomedical research and clinical findings in the residents of the Marshall Islands, the occupants of the Japanese fishing boat that received fallout in quantity because of an unpredictable shift in winds at high altitudes, and some of the sociological and psychological overtones of these events. We describe, largely by reference to the work by the University of Washington Fisheries Laboratory and collaborating groups, the surveys of the Marshall Islands for residual contamination and the movement of radionuclides in the ocean. We also review in some detail the several oceanographic expeditions mounted by Japanese and American investigators and organizations and

the knowledge they gained regarding movement of radioisotopes in the marine environment, possible effects on aquatic biota, and the possible contamination of food from the sea.

To introduce the study of fallout behavior and effects in terrestrial environments, we look first at the well-designed and informative resurvey of the Trinity site. We turn next to nuclear weapons testing in the continental United States at the Nevada Test Site. The early experiences in mapping fallout and early biological information from the Nevada Test Site set the stage. The most extensive discussion concerns offsite contamination from the Nevada tests. It proceeds from the first realizations that such contamination was occurring through the sudden appreciation of the role of food chains in bringing contamination to man, through clinical studies of the populations to the final stage, litigation. The saga of the large sheep herds is also considered, plus the onsite exposures of military personnel involved in training exercises ("Atomic Veterans") and onsite workers.

The summation of the fallout from the Nevada tests and the injection into and slow release from the stratosphere of radionuclides from the Pacific shots into the entity we call "global fallout" is discussed next. It is necessary to devote considerable attention to the physical events and measurements, to the somewhat unorthodox dosimetry introduced by the Sunshine Project, and to correlative federal and international programs. The biomedical aspects of global fallout are described by considering the radionuclide content of important biological materials and the large questions of contamination of food and water, discrimination factors, and protective actions.

Although details of protection standards for radionuclide exposure are contained in chapter 16, the application of these to environmental contamination, particularly to radionuclides from fallout, was considered to require specific attention in this chapter. Thus, there is a section devoted to radiation protection standards from fallout. Emphasis is placed on the development of exposure standards for populations, the identification of special problems, and the development of both radiation protection guides and protective action guides by the Federal Radiation Council.

The chapter concludes with a recitation of some of the principal dilemmas and problems of the fallout experience. It includes the question, "Should we have tested?"; the role of the hidden doses (i.e., doses from fallout radionuclides not included in the usual routine measurement of external radiation); and an exposition of the crusade of Ernest Sternglass on fetal and infant mortality that began around possible effects of fallout. Finally, there is a short review showing that, despite the myriad problems introduced by the fallout situation, it was responsible for some significant progress in the fields of biology and medicine. This will be more apparent in chapter 13. Because of the enormous amount of work done and the voluminous publications on fallout problems, the chapter is devoted primarily to work done by U. S. investigators. However, from time to time the contributions of investigators and organizations in other countries are introduced. Sometimes these are described as part of an ongoing discussion, sometimes under a separate heading.

I. Introduction

In chapter 6, we met "New Dimension Number One—The Fission Products" and in chapter 7, "New Dimension Number Two—Plutonium and the Transplutonic Elements (The Actinides)." The first was a new dimension by virtue of the

addition of hundreds of new isotopes of elements already known for the most part as stable rather than radioactive elements. The second posed a new dimension by introducing a whole new family of manmade elements whose biological behavior and effects had to be ascertained. These were new dimensions primarily to science and technology. The third new dimension, "Fallout from Nuclear Weapons Testing," the subject of this chapter, added not only new scientific and technical problems but problems of the first magnitude in the political and military arenas. The gradual perception of these problems and what they were is the subject of this chapter.

Over the thirty-year period beginning in 1945, more than 800 tests of nuclear "devices" were carried out by the six nuclear powers. The announced totals are: United States 579, USSR 136, United Kingdom 26, France 43, People's Republic of China 16, and India 1. The majority of the tests centered on weapons development. However, a few were directed toward the uses of nuclear explosives for peaceful purposes, such as digging harbors and canals and related applications. (Details are in chapter 14.) The total energy yield in kilotons (kt) of TNT equivalent was over 325,000, divided roughly as follows: United States 77,500 kt, USSR 207,000 kt, United Kingdom 18,200 kt, France 7,000 kt, People's Republic of China 15,500 kt, and India 13 kt. Obviously, the United States carried out a much larger number of relatively small tests than some other countries. Indeed, some U.S. tests were very small indeed.^(a)

Because it was testing in the atmosphere that contributed the most to fallout, it should be remarked that, of the total yield of 325,000 kt, approximately 270,000 kt (370 tests) were in the atmosphere. Second in significance to the understanding of the importance of fallout problems were the underwater tests, even though there were only six of these, with a total yield of 90 kt. The later underground shots are not included in this summary.

Details on the statistics described above can be found in a review by Carter and Moghissi (1977) with a commentary by Richmond (1978) and in U.S. government publications (e.g., NVO 1982).^(b)

We saw in chapter 6 that the fission products consist of a complex mixture of radionuclides whose radioactivity decreases rapidly with time. There are many isotopes present with very short half-lives and many products that are themselves the progenitors of a chain of daughter products. Also, some are gases initially but become solids on decay to a subsequent degradation product. As discussed briefly in chapter 6, such a complex mixture of substances, each decaying exponentially with time, presents a composite decay curve that can be

(a) Remember that the bombs that devastated Hiroshima and Nagasaki were nominally about 20 kt. Also note that these figures do not include relatively recent tests.

(b) Thanks are due especially to Gordon Facer, Bruce Church, Marshall Page, Jr., and colleagues for making these available, relatively soon after declassification in some instances. The location of the several test sites, code names with dates, and a few characteristics for all of the announced tests to date of publication of the United States, the United Kingdom, and France, and the dates for Soviet, Chinese, and Indian tests are also given by Carter and Moghissi and in the U.S. government report cited. Much greater detail was made available to me through the Division of Military Applications of the Department of Energy (DOE) and the document center at Las Vegas, Nevada. These include the paths of the fallout, radiation dose contours as a function of time and distance, and much else that cannot be described except in general terms in a book with so broad a mission as this one.

represented as a power function of time, e.g., most characteristically as $(\text{time})^{-1.2}$. The exponent may vary from -1.1 to -1.4 depending upon the exact construction of the device.

The predominant early radiations are beta particles and gamma rays. Thus, the chief early biological hazard from fresh fission products is usually external radiation.^(a) Hazards from internally deposited fission products arise somewhat later.

Fallout from weapons tests consists primarily of these fission products, plus from enormous to small amounts of dust and debris depending upon the altitude and conditions of the burst. (Obviously, a surface or near-surface burst will entrain much more of these than a high-altitude detonation.) In addition, gravimetrically small but biologically significant quantities of unfissioned alpha-particle emitters from the device and relatively large amounts of radioelements produced by neutron activation of elements in the device and in the environment will be present. In the case of the fission-fusion devices (the "hydrogen bomb"), quantities of tritium and other products special to this process will also be included.

In chapter 6, we referred to Glasstone's *Sourcebook on Atomic Energy* among others for details on the formation of fission products and their characteristics. For their behavior in fallout from nuclear weapons, the standard reference is Glasstone's *The Effects of Nuclear Weapons*. This has gone through three editions, the most recent of which is Glasstone and Dolon (1977). Therein can be found detailed expositions of the major components of a nuclear explosion, i.e., blast, heat, and radiation; the patterns of fallout, both local and global;^(b) how to calculate the external dose at any given time as well as the dose to infinite time; and much more. Many other sources are, of course, available, including short summaries in numerous texts, the monographs cited in chapter 11, and exhaustive discussions in the many Congressional hearings called as the dimensions of the problems of fallout became more and more apparent (U.S. Congress 1955, 1957, 1959, 1962, and 1963). A very useful review of research around the problems of fallout was prepared recently by Book and Goldman (1983) for the Department of Energy. This provides a check-back system for the major enterprises.

Let it be emphasized that the composition of and problems from initial fallout from weapons are quite different from those that might be encountered in releases from a nuclear reactor (see earlier chapters). It is only after a period of aging of the fission products that the characteristics and problems begin to approach each other. The external radiation dose predominates in the early

(a) The devices also produce neutrons that add to the external dose, but these do not arise from the fission products themselves. Inhalation of iodine isotopes can also be an early hazard.

(b) Glasstone and Dolon describe the three major classes of fallout (local, tropospheric, and stratospheric) in detail. The organization of this chapter is somewhat around these classes in that most of the earlier problems were local with a small component of tropospheric transport, e.g., Trinity, Hiroshima, Nagasaki, Crossroads. The Nevada Test Site experience, on the other hand, had a much larger component of tropospheric contamination, and the major Pacific tests had a large component of stratospheric contamination and transport.

phases of fallout even more than with reactor fission products, a fact that underlies some of the apparent neglect of internal doses in considering weapons fallout that has become a source of recent concern.

With the cessation of atmospheric testing and the substitution of tests deep underground, the furor of the 1950s and 1960s died down, and only the specter of nuclear war kept the fallout issue alive.^(a) However, the recent development of litigations concerning possible effects of the fallout from atmospheric testing on populations in the continental United States, including the "Atomic Veterans" (U.S. Congress 1980) and the institution of retrospective analyses, have led to a wide-ranging and thorough reopening of the files on the whole story. The U.S. government has established a Coordination and Information Center at the Nevada Operations Office of the Department of Energy in Las Vegas, and thousands of documents are now available, many of which were classified until recently.

There is enough information in these many sources to write a complete book. We will look in this chapter primarily at the historical development of the information and touch lightly at the end on some of the current activities. (The touch will perforce be very light in areas still under litigation.)

The adequacy of the safety measures taken around the tests is at the heart of much of the current polemic. This subject is hardly research, if rigidly defined. Nevertheless, the present compendium would have been forced to enter that arena in some detail were it not for the parallel development of an independent treatise on the safety measures associated with the testing program. Dr. Barton C. Hacker, a historian from the University of Oregon, used interviews, the enormous resources of the Coordination and Information Center, and files of several laboratories to prepare a book, under DOE auspices through the Reynolds Electrical and Engineering Co., Inc. in Las Vegas.^(b) This much expanded and detailed complement to this chapter will trace the various tests almost day-by-day and decision-by-decision. Many of the chapters have been made available to this author already and have provided background for some of the data presented herein. Other descriptions are in the source material cited in chapter 11, especially in the book by Hines (1962).

Let us reiterate that this chapter will concentrate on the tests and the biomedical work done in more or less direct association with them. Later chapters will describe research arising out of the problems produced by the generation of fallout. It should become clear that fallout from nuclear weapons testing provided not only a new dimension for chemistry, physics, biology, and medicine but one of the most significant challenges and boosts that environmental science has ever received. What the physicists and engineers wished to learn and the concomitant development of weaponry are not part of this treatise. Much can be learned from the several biographies and histories cited from time to time (see especially Appendix B).

(a) Along with the continuing survey of the Marshall Islanders to be discussed presently.

(b) The first volume of this compendium was published in 1987 (Hacker 1987). It covers the period of World War II plus Operation Crossroads. This volume (published by the University of California Press, Berkeley, and Los Angeles) is entitled *The Dragon's Tail. Radiation Protection in the Manhattan Project, 1942-1946*.

II. The Story Unfolds

A. Trinity (Alamogordo).

The military aspects of the atomic age burst upon mankind,^(a) for better or worse, at 5:30 a.m. on July 16, 1945 in open desert not far from Alamogordo, New Mexico. This was a test of a plutonium-based device, frequently referred to as "the gadget," atop a 100-ft tower, the climax scientifically and technically of the years of effort expended in the Manhattan Engineer District (MED).^(b) There are hundreds of accounts of that event. A firsthand one written by the ace science reporter from the *New York Times*, William L. Lawrence, is both dramatically readable and basically accurate.^(c) (Lawrence 1959).

As we all know, the results were beyond expectations and filled the observers with awe at the dimensions of what they had done, with pride in the success of their work, and with misgivings for the future unless controls were rigid.

The dimensions of the blast and fireball and the phenomenon of prompt radiation eclipsed, for the casual observer, the more subtle possibilities of fallout. Indeed, not much was heard about fallout from the Trinity shot except in scientific circles until some years after the event.^(d) This has led, in some circles, to the erroneous idea that the MED bomb developers, even the biomedical contingents, were unaware of the potential for more than the prompt radiation release. This was totally untrue, although it is true that only shortly before the test did the calculation of potential fallout reach disturbing magnitudes.

The device was to be detonated close to the ground, and a towering cloud of dust with fission and activation products had to be considered possible. The weather conditions selected for the shot were predicated mostly upon the possible direction such a cloud might travel.^(e)

An extensive monitoring program was set up for Trinity, as part of a broad safety program under the general direction of Louis Hempelmann and the Los Alamos Health Division, with much help from the military. This involved not only intensive work around the site but monitoring offsite and contingency plans for evacuation of the public should the cloud fail to break up as expected or pass over inhabited areas. Hymer Friedell, deputy director of the Medical Division of the MED, had to forego witnessing the test in order to be in a hotel room in Albuquerque ready to communicate to military teams stationed surreptitiously in towns potentially subject to cloud passage to order evacuation if levels at any of them reached alarming proportions.^(f) (See Hacker 1987.)

(a) In a sense, we might say that the atomic age began with the discovery of radioactivity and radium (chapter 1).

(b) A ^{235}U device was ready also but was saved for use in Japan.

(c) Lawrence was the only press writer invited to witness the test. It was considered important that the media be prepared for the planned bombings of Japan if "the gadget" worked. Lawrence was well known to the physicists and was trusted.

(d) It is given proper coverage in Lawrence's book (1959), but that was over a decade later.

(e) The weather conditions for the shot had to take second place to the date for opening of the Potsdam Conference. President Truman wanted to know on or before the day it opened (July 16!) whether or not America had a trump card to play.

(f) Obviously, if evacuation was needed, the real reason could not be given to the residents since security was still very tight. The story would be that an ammunition dump had exploded and there were gas shells in the dump.

Security was still of the essence. Therefore, the level of radiation at which evacuation would be undertaken was chosen to fit only a true emergency pattern. This was much discussed beforehand. Hempelmann and the Los Alamos staff, plus Stafford Warren (see earlier chapters) and advisors from Washington chose a potential calculated integrated dose of 68 roentgens in two weeks as the action level (references are given to original correspondence by Hacker undated). Warren, a practicing radiologist, was reputed to have considered a peak rate of 10 roentgens per hour acceptable if the calculated potential total did not exceed that given above. These are, of course, far beyond any levels that would be tolerated currently for exposure of the public. However these were still wartime conditions. Maintaining the secret forced some compromises with safety, although even today it seems unlikely that any overt short-term effects, certainly no radiation sickness, would have appeared had the peak levels been reached.

Fortunately, no inhabited community of any size received fallout even approaching the level that would have triggered evacuation. Only one area, relatively close to the site, achieved moderately high levels. High readings were found in an area northeast of Bingham, New Mexico, especially along a road running through a steep gorge later nicknamed "Hot Canyon" (Hacker undated). Also, two isolated ranches, not on the maps and not discovered by the military teams before the shot, were discovered in this area. The families on these ranches were monitored carefully. The maximum whole-body accumulated dose for twelve weeks was about 50 roentgens. This was estimated on the basis of readings taken outside of the adobe dwellings and applied really only to one man. The others were indoors most of the time. Evacuation was not considered necessary.

The chief victims of Trinity turned out to be animals and some photographic film. A dog belonging to one of the families above showed clear evidence of beta radiation burns on the paws. Range cattle on a high grassland called Chupadera Mesa turned up with burns on their backs and falling hair that grew back discolored, or, white—not a life-threatening effect but a sufficient loss in market value that the Army bought any cattle the ranchers wanted to sell. It was estimated that about six hundred cattle were affected. About seventy-five were shipped off to Oak Ridge for long-term study and became the basis for the University of Tennessee-Atomic Energy Commission Farm to be described in chapter 13.

Veterinarians confirmed that the lesions in the cattle were classic beta burns and that they had been caused by fallout from the Trinity shot. The fact that no similar effects turned up in the few humans in the Chupadera Mesa area can be attributed to the fact that few were out-of-doors at the time of cloud passage, humans wear clothes, and they bathe. By contrast, the hot particles settling on the coats of the cattle worked down to the underlying skin and remained there. Estimates of the dose to their skin were in the thousands of roentgens. The story of the photographic films came from the Eastman Kodak Company in Rochester, New York and indicates that some fallout had strayed far from the Alamogordo site. During August of 1945, batches of photographic film began to show areas of fogging and spots such as those shown in figure 12.1.

A perceptive physicist named Julian Webb at the Kodak Research Laboratories traced the phenomenon to the black interleaving paper used to separate films in the package. He further traced it to paper made from corn husks from a field in Indiana (Webb 1949). He also deduced that these particles could have

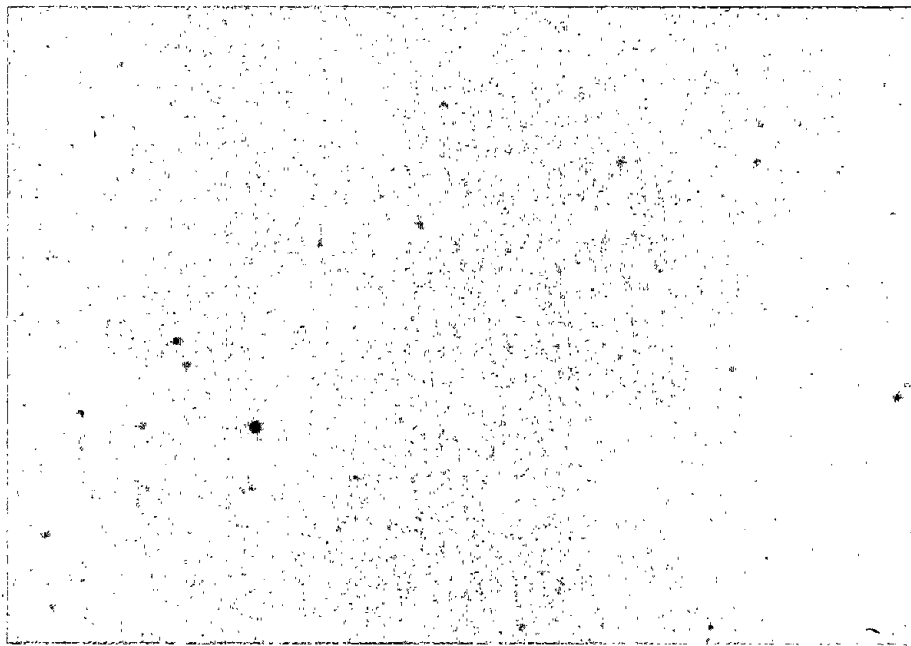


FIGURE 12.1: Eastman Kodak film affected by the fallout from the Trinity Shot, Alamogordo, New Mexico, 1945. The interleaving paper had been contaminated by fallout in Indiana. (Original by Webb [1949]. This copy from Eisenbud [1976] via Kathren.)

reached that cornfield only by transport in air and that some sort of explosion had injected them into the atmosphere. Indeed, he concluded that it was an atomic device—not bad considering the secrecy still pervading the operations, but not unexpected from Julian Webb. He patiently held his counsel and did not publish on the subject until 1949.^(a)

In view of the complete novelty of the experience, the relatively few experienced monitors, and the relative antiquity of both communications and measuring instruments, it was indeed remarkable that anything was learned about the fallout offsite as well as onsite in connection with the Trinity shot.

Back at ground zero, crews in lead-lined tanks were making forays up to, sometimes into the crater and were retrieving samples of a glassy substance that was very highly radioactive (later called “Trinitite”). The residual activity in the crater greatly exceeded expectations partly because the calculations had underestimated the amount of neutron activation that would take place.

No one in an official capacity seems to have been hurt by these very hot samples. However, after things opened up a bit, many adventitious forays by rank and file military were made into the crater to collect souvenir samples (shades

(a) Obviously, Webb was not the only one at Kodak who knew something of the MED. It was Kodak that ran the Tennessee Eastman uranium processing plant at Oak Ridge. Kodak people played an important role in persuading Stafford Warren to leave the University of Rochester to become medical director of the MED, e.g., Dr. Albert Chapman, president of Kodak.

of Becquerel carrying Madame Curie's gift of radium in his vest pocket; see chapter 1). Louis Hempelmann put a stop to that instantly when he learned of it.

In retrospect, two gaps appear in the descriptions of Trinity. There was clearly residual plutonium, since efficiency was not one hundred percent. This should have been present partly in the crater, partly scattered about the environs with the fallout. A full-scale resurvey of the Trinity site was carried out three years later by the group at the University of California, Los Angeles (UCLA), medical school, as will be described in a later section. They did indeed find some plutonium. It was not measured very carefully at shot time, although its presence was hinted at in the initial surveys.

The other gap is the lack of any measures for detection of internally deposited radionuclides, e.g., bioassay, nose swabs, etc. Perhaps bioassay was performed when the individuals returned to their home stations, but such data are not included in the story of safety around Trinity. Obviously, concern focused on immediate hazards, and the monitoring methods were geared to measurements of beta and gamma radiation except for a few alpha counters that were used onsite. The thinking had not yet focused on possible long-term effects.

We must conclude that, despite the overwhelming magnitude of the other aspects, the light, the heat, the blast, fallout both close-in and distant was not neglected in the Trinity operation. Indeed, its potential was highlighted "in house."

B. Hiroshima and Nagasaki

The bombs exploded over the two Japanese cities were detonated at altitudes high enough to entail little entrainment of dust and debris. The immediate problems were largely blast, heat, prompt radiation, and residual radiation caused by neutron activation. Fallout as defined herein was considered a minor component of the events.

Nevertheless, there was some fallout at a distance. Little was said about this until in later years the Japanese pinpointed the areas of highest dose and did a thorough study. Okajima et al. (1978) reported a study done in collaboration with the Atomic Bomb Casualty Commission and the Nagasaki University School of Medicine on individuals, soil, and crops in the Nishiyama area. This area received the highest dose of fallout from the Nagasaki weapon. Whole-body counting and urinalysis for ^{137}Cs showed a significantly greater concentration in the exposed subjects. It was determined by soil and crop analyses that these increased levels were supported by continual ingestion of radiocesium. (The effective half-life of ^{137}Cs is much too short for the amount found in the inhabitants to have been residual from deposition in the body in 1945.) Physical examination and laboratory analyses, including tests for chromosome aberrations, showed no large increase in abnormalities in the exposed compared to the control subjects. Two groups were studied, one in 1969, the other in 1971.

The populations of the two Japanese cities have provided enormously important and useful data on the effects of gamma and neutron radiation in humans exposed at high doses and high dose rates.^(a) However, it is all germane to external radiation and has little pertinence to the mission, and focus of this book, internally deposited radionuclides.

(a) It is a monument to the spirit of all concerned that so much useful information could be gathered from the residuum of tragedy.

C. Operation Crossroads—The Dimensions Expand

In the flush of excitement over the new atomic weaponry and a mixture of a desire to know more about what such weapons might do to a naval task force and a desire to demonstrate the awesome powers involved, "Operation Crossroads" was developed. In contrast to all previous operations and the close security of the Manhattan District, this was almost a public demonstration. A shipload of press correspondents and other observers was present, and numerous dignitaries were invited.

The events took place in June and July of 1946 at Bikini Atoll in the central Pacific Ocean (figure 12.2A and B). It was a joint Army-Navy task force, primarily a Navy show in terms of the targets and operational questions to be solved. It involved 42,000 men and women, 242 target and support ships, and 156 military aircraft (Hacker 1987; Hines 1962, chapter 2), all some 4,500 miles from continental America.

There were two detonations; one an air drop from a B-29 aircraft about five hundred feet above the assembled target vessels^(a) in the tranquil lagoon. The other was an underwater detonation at a depth of about ninety feet below an assemblage of wartime ships. Both had yields approximating those of the Hiroshima and Nagasaki weapons. One objective besides assaying damage to naval ships was an evaluation of the importance or lack of it of contamination from fallout in denying access to and operation of exposed vessels.

"Radiological safety in so huge an undertaking at so remote a site posed massive problems" (Hacker 1987). The MED assumed responsibility, and Stafford Warren headed the Radiological Safety Section. This time, Los Alamos H-Division could not supply all of the manpower needed. All MED labs were asked to contribute manpower and equipment for monitoring and maintenance of safety.^(b) Some friendly, and some not-so-friendly competition developed among the labs as they began to gather their equipment for the operation. This was, to a degree, the first time the labs had worked shoulder to shoulder and had theoretically to trust the instrumentation developed by others (Andrews 1980). However, the organization was tightly military, and such problems were handled by fiat.

The radiation safety aspects are being described in depth by Hacker and will not be expanded upon here except to comment that it was ruled that workers should not have total exposures over 50 to 60 roentgens in two weeks or more than 10 roentgens in one day.

On the biomedical research side, there were several projects. The University of Washington group studied aquatic biology of the region pre-shot and gathered a variety of samples post-shot. Test animals were placed on over twenty vessels for Test Able at various distances from ground zero.^(c) These were retrieved in two days post-shot. There were 200 pigs, 60 guinea pigs, 204 goats, 5,000 rats, and 200 mice (Hines 1962, p. 35). Good laboratory facilities were afforded by the hospital ship, USS *Haven*, which became a focus for the biomedical program.

The air drop test (Test Able) contributed more to the understanding of acute radiation effects than to those of fallout. The underwater test (Test Baker) produced the first full realization of how much contamination could be produced

(a) Unfortunately, somewhat to the side of the intended ground zero.

(b) Chicago, Oak Ridge, and Rochester contributed many individuals.

(c) The test animals were under the supervision of Captain R. H. Draeger, USN, from the Naval Medical Research Institute in Bethesda, Maryland.

by a nuclear bomb burst in sea water. Not only did the waters of the lagoon become highly radioactive, but tons of heavily contaminated water thundered onto the target fleet from the 2,200-ft diameter column of water. Much of the radioactivity became fixed to the metal. Even ships that did not receive contaminated water showered from above became contaminated by a radioactive mist from the base surge.

The early drone planes that entered the area for radiation readings after Test Baker reported levels of activity of such high intensity that no human could enter for more than a few minutes. Surface patrol boats soon had to turn back also. The activity levels were far above predictions. Salvage efforts were slowed or abandoned, and ships that might otherwise have been saved were flooded. It was three days before radiation levels in the lagoon had decreased to the point where salvage efforts and recovery of instruments and animals could begin in earnest. For Test Baker, there were twenty pigs and two hundred rats on four ships. Mortality was high, partly because of the longer exposure times and higher doses resulting from the delays in retrieval.

Contamination spread to vessels not in the target array. If they entered the more radioactive lagoon water, the activity attached itself by strong chemical bonds to the metal and also was taken up avidly by the ever-present barnacles^(a) on the hulls. Thus, being below decks did not necessarily afford protection. Many of the ships had to be towed from the anchorage, not because of structural damage, but because they were too radioactive to permit crews to board and operate them.

The first tows were to Kwajalein, which had to become the new base for operations because of the persistent radioactivity in Bikini Lagoon. Eventually all ships involved that did not sink or have to be beached received decontamination, but the results were disappointing. The techniques required were much more than a simple hosing down. From this eventuated the Naval Radiological Defense Laboratory (NRDL) on Hunters Point in San Francisco Bay, since that area became a repository for many of the Bikini vessels. (See chapter 13 for details.)^(b)

(a) The term "barnacles" is used loosely as a generic term for the many organisms that attach to hulls of ships. A more accurate term might be "fouling organisms" because they may or may not have been true barnacles in this instance. However, most landlubbers call all such organisms attached to ships "barnacles" and that is why it is used here.

(b) During the interval between the Baker experience and full functioning of the Naval Radiological Defense Laboratory, the Armed Services, particularly the Navy, mounted an intensive training and education program. Only a small number of competent lecturers were available for such a program. Among them was H. L. Andrews of the U. S. Public Health Service. He appears to have spent many months almost full time in elementary shipboard training and then intensive courses at the main Navy building and elsewhere in Washington (Andrews 1985). This was coordinated by the Armed Forces Special Weapons Project. Interestingly, the notes and syllabus from these courses developed by Andrews with help from Ralph Lapp formed the basis for the highly successful text, *Nuclear Radiation Physics* by Lapp and Andrews used very widely for decades. Obviously, while facilities for attacking the problems experimentally were being readied, the word was being spread, mostly under tight security restrictions. The burden of specific training in the new field remained in the hands of the Armed Forces for many years. A further insight into the training efforts of the Armed Services during this period of hiatus in other quarters can be found in the transcript of a television interview between H. L. Andrews and L. S. Taylor, done in August, 1978. The entire series has been published recently by the Food and Drug Administration (Taylor and Sauer 1984). Dr. Andrews' remarks appear on page 5.

Not much can be said about the animals aboard the target ships for each test. They were necropsied in laboratories aboard the *Haven* or saved for observation. Acute radiation syndrome was probably all they found. Many were already dead. A description of the necropsy findings is given by Tullis and Warren (1947). The lesions were typical of high-dose ionizing radiation.

By contrast, the radiobiological survey team under the leadership of Lauren Donaldson (University of Washington) could get specimens of sea life from large fish to the smallest plankton without having to proceed into the most highly contaminated areas.

These were subjected to radiochemical analysis in the laboratories on the *Haven*. The algae proved to have the highest activity; fish that fed on algae also had high activity (Hines, p. 44). Thus began a saga of measuring and following the behavior of radioactive contamination from fallout in an aquatic system that continued for many years. In the earlier years, the measurements were made largely by Geiger-Müller counters. There was little opportunity for identification of individual radioisotopes, and sensitivity was not high. Also, alpha emitters may have been missed. As the work progressed, the sensitivity improved, and there were opportunities to identify individual radioisotopes. We have reported the results in terms of the capabilities of the instruments in use at any given time. The reader should take this into account as the work unfolds.

For the short term, the activities found in all organisms around the lagoon led Welander (letter report quoted by Hines) to recommend that no fish, mollusk, or other marine animals taken within one hundred miles of Bikini Lagoon be used as food!

Some evidence developed that organisms were beginning to die on the north reef between Bikini and the adjoining Aomen Island. However, the operation was winding down, the support vessels and personnel were departing. All that could be done was to pack up the specimens for later examination and write a long list of things requiring additional study.

Operation Crossroads was intended as partly a demonstration to the assembled observers of the awesome power of the atomic bomb. Test Able disappointed many. Test Baker left no doubts. Test Baker also brought the potential problems of short- and long-term contamination from fallout vividly front and center. Fortunately, through careful planning, no human being was seriously contaminated or hurt by the radioactivity in these operations. Kudos go to all concerned, particularly the personnel from the medical department of the MED and the medical and support staffs from the U.S. Navy with help from the Public Health Service (PHS) and the Army. (a,b)

(a) *Note added in proof:* It now appears that contamination of men assigned to scrubbing down the decks of ships for Test Baker may have been greater than hitherto reported. Also, the dosimetry, especially a possible greater amount of contamination from alpha particles, and large errors in reading film badges have been brought up for further question (Marshall 1985). Some of this re-examination was stimulated by the opening of the files of Stafford Warren. It will probably continue. Nevertheless, these retrospective doubts do not negate the fact that the enormous dimensions of the operation, much beyond expectations, could have produced a serious debacle without the efforts of the biomedical community, naive as they now seem.

(b) *Second note added in proof:* A very readable retrospective review of Operation Crossroads appeared in a review by T. M. Daly (1986), as well as in the book by Hacker (1987).

III. The Pacific Proving Grounds

A. Overview

On the completion of Operation Crossroads, it was expected that the Bikini Atoll and all of the central Pacific could return to placid somnolence. There were some doubts about how soon the Bikini residents could return to their island, but it would have to be as soon as possible, for a commitment had been made. All of that was before it became clear that the Russians had detonated an atomic bomb (announced on September 23, 1949, by President Truman); before the realization that it would be relatively easy to tap the enormous power of fusion; before the Korean War; and before the Cold War. These events made it clear that testing of atomic weapons was far from over and that a remote site would be needed for testing of larger weapons, including hydrogen bombs, should such be developed. After consideration of many possible sites, including Alaska and the Indian Ocean, the decision was made to establish a proving ground back in the central Pacific in the general area already used in part but greatly expanded. (For details see Hines 1962, chapter 4.)

The development was, of course, gradual. There was first a resurvey of Bikini Atoll under the sponsorship of the new Atomic Energy Commission (AEC). This was planned before the decision to establish a Pacific proving ground. The enterprises were shifted from Bikini to Enewetak, partly because of the lingering radioactivity found on Bikini and partly for operational advantages. A map of Enewetak Atoll is given in figure 12.3.

The first tests were of fission devices and were centered mostly on improvements of design and efficiency. There were three shots in the Enewetak area in operation Sandstone, carried out in the spring of 1948. Yields ranged from 18 to 59 kt. Biomedical studies were not emphasized in this series, although there was some ecological work, and considerable aquatic biology was performed.

An interim of three years followed before any other major tests took place in the Pacific. This gave a very useful opportunity for the biologists to follow through on sampling of flora, fauna, and water for both radioactivity and possible development of biological effects. Then in 1951 came the "Greenhouse" series, in 1952 the "Ivy" series, and in 1954 the "Castle" series. By this time, we were well into the testing of thermonuclear devices, and the true dimensions of potential problems from fallout became very evident, especially with the 15-megaton "Bravo" shot.

Two years later, "Operation Redwing" took place at both Enewetak and Bikini with a few announced yields in the megaton range but none as large as the Bravo shot. After another two years, "Operation Hardtack" took place in two phases with Phase I at the Pacific Proving Ground. This involved not only Bikini and Enewetak, but also Johnston Island.

All of these detonations were in the decade of the 1950s. Few of them had overt biomedical objectives, but some enormous problems were forced upon the biomedical community by these events. This section will review primarily the biomedical aspects of the Pacific tests.

B. The Resurvey of Bikini

The biologists, most of them from the University of Washington Applied Fisheries Laboratory, were keenly aware at the end of Operation Crossroads of the need for follow-up at Bikini. The opportunity came sooner and more easily than

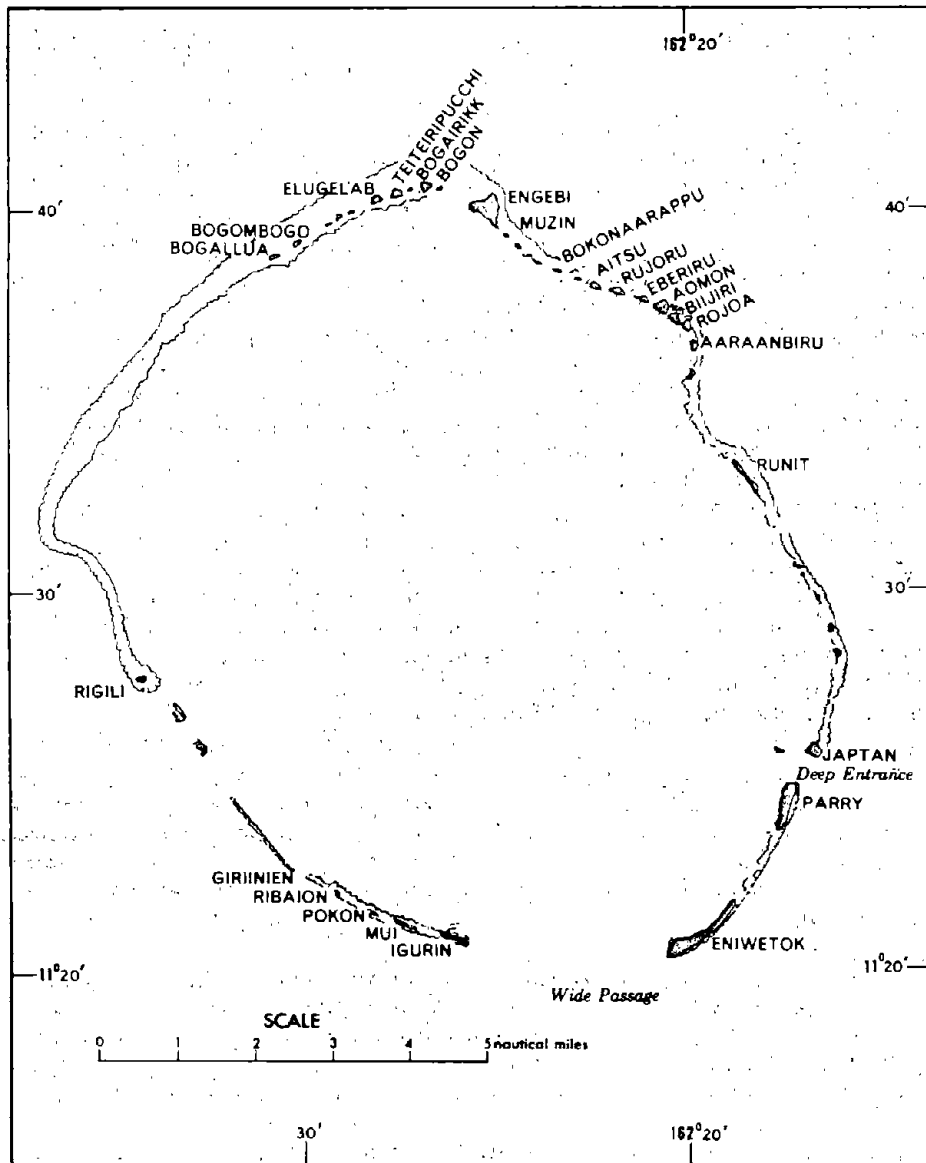


FIGURE 12.3. Eniwetok Atoll. (Modified slightly from Hines 1962. Reprinted with permission of University of Washington Press, Seattle, Washington, copyright 1962.)

expected, as Hines describes (chapter 3). The first resurvey became possible in the summer of 1947.

This operation included the fisheries group already described plus representatives from the U.S. Fish and Wildlife Service, other universities in addition to the University of Washington, the Hopkins Marine Station, the Scripps Institution of Oceanography, Oak Ridge, and others. A moderately large ship, the

Chilton, based at the San Diego Naval Station, carried the assembled group plus two radiochemistry survey facilities, a counter room, a fisheries laboratory, and an experimental biology laboratory. Some of the equipment was moved ashore on arrival at Bikini. There was one laboratory ashore devoted to morphological and physiological studies of plants and one for marine invertebrates. There were also accommodations for groups doing low-level radiation studies, geology, and aerology (Hines 1962).

The first observation came immediately on re-entry into the lagoon. The water that had been light green and crystal clear before the Baker shot was turbid and like mud in color. This phenomenon seemed to reside in suspended small particles from the grossly disturbed bottom. These particles kept picking up radioactivity from the sunken vessels and bottom sediments and in turn passing it on to the plankton residing therein and to larger organisms feeding on the plankton.^(a)

The chief interest was, of course, the extent and nature of the residual activity. There was ample evidence of very widespread residual radioactivity. Fission products were found in clams, snails, oysters, corals, sponges, octopods, crabs, sea urchins, sea cucumbers, spiny lobsters, shrimps, and in the fish caught in various areas. Concentrations in the fish were greatest in spleen, liver, and feces, followed by kidney and gonads. Highest contamination was still in the area of the detonation, but the profiles had extended much more widely than at the end of Operation Crossroads. Later there was increased emphasis on the presence of residual alpha-particle contamination from the devices.

None of the levels was considered high enough to produce acute radiation damage in any of the organisms. Examination of over one thousand species (tens of thousands of specimens), many of them having reproduced through one or more generations, failed to reveal evidence of aberrant forms, nor was there evidence of interference with reproduction. However, the marine ecosystem is not an easy one in which to spot any but large changes, and conclusions were very guarded.

There was reassurance in the finding that strontium and cesium, the most feared fission products, appeared to be absent. Plutonium was found, but in small quantity.

Nevertheless, the levels of radioactivity found were sufficient to raise doubts about the speedy return of the Bikini residents. The possibility of long-term effects and concentration of radionuclides in foodstuffs could not be denied. Furthermore, the biological data had raised as many questions as they had answered about the transport of radionuclides in such a diverse and complex ecosystem.

On their return home from the six-week summer sojourn, the laboratories worked hard on examination and measurement of the materials collected and on analysis of the data. One firm conclusion was that a further resurvey should

(a) Dr. Allyn Seymour (personal communication, June 1985), who was a member of the Bikini resurvey group, remembered these phenomena, but with slightly different timing. He recalled that the water was turbid and green at the end of 1946, but it was not very turbid in 1947. He also inclined toward the view that the phenomena may have been more due to overgrowth of plankton from nitrogenous waste deposits by personnel of Operation Crossroads than to direct results of Test Baker. Hines (1962) also mentions this possibility. In any event, things had changed.

be undertaken in the summer of 1948. They pointed out that "only through continuous long-term effort can we hope to understand the basic principles involved" (Navy Department 1947).

This further resurvey was accomplished, but on a much smaller scale because of activities at other atolls of the Pacific Proving Grounds. Many of the key personnel were invited to observe the new tests at Enewetak, and they had opportunity to collect marine specimens from some of the islands, e.g., Runit.

We will save further details of the aquatic biology and ecology findings for a special section.

C. Sandstone, Greenhouse, and Ivy

We will not attempt to recount step by step the biological efforts and findings associated with these three series of shots that went from the kiloton into the megaton range. Such a step-by-step analysis has been masterfully done by Hines. The radiological safety aspects will be made available in much detail by Hacker. We will instead enumerate a few highlights:

1. More detail could be discerned as instrumentation potential proceeded from permitting only gross beta radioactivity and crude measurements of alpha contamination to the separation of radionuclides and much greater sensitivity.
2. In 1949, a group was carried on a small ship (LSJ[L]1091) from Kwajalein to Bikini and then to Enewetak for sampling of everything possible.
3. Much more detail concerning radioactivity and possible effects in plants became available.
4. Studies were begun on animal life of the atolls, e.g., rats, coconut crabs.
5. Local coconuts and other crops contained residual activity greater than twice that of crops from outside the area.
6. The final shots of Sandstone were marred by the occurrence of beta burns in personnel removing air sampling filters from the cloud-sampling drones landing at Enewetak. The activity levels demanded abnormal haste. The members of the Radiochemistry Group had no relief workers to call upon and evidently cut corners by using gloved hands alone instead of gloved hands plus tongs, etc. (Hacker undated). These individuals were relieved of duty in the field and went back to Los Alamos along with the samples. They may represent the only cases of beta burns from fallout since the Alamo-gordo cattle.
7. Some aberrations in plant growth were found on Enewetak fifteen months after Sandstone. Some of the plants showed structural abnormalities, while others exhibited a physiological change called "die-back." The plant would begin to grow vigorously, but the young stems would turn yellow and the entire plant gradually wither back to its roots. Yet, the plants in the early stages produced viable seeds that went ahead and began growth only to wither back in turn. Unfortunately, these aberrations could not be ascribed definitely to radiation. They resembled phenomena such as calcium deficiency, a process that could not be ruled out in the close-in areas where the aberrations were most pronounced.
8. A few tumors appeared on plants near the Enewetak shots. It appeared that, if they were radiation induced, they were caused by direct radiation from the surrounding soil, not uptake of radionuclides through roots or leaves.

9. The Greenhouse tests in 1951 involved little return to the aquatic biology programs. Instead, animals (mice, dogs, and pigs) were exposed to the radiation and other effects of the blast, primarily to aid the development of treatment methods for atomic bomb casualties. Since this involves primarily external radiation problems, it will not be expanded upon here except to quote the opinion of Lieutenant General E. R. Quesada, U.S. Air Force, Commander of Joint Task Force Three as follows:

We have again operated in and around radioactivity. Our operations have indicated to us clearly that the mysterious ghost of lingering radiation should be dispelled. The immediate radiation, blast, and heat kill and destroy. Fear of lingering residual radioactivity must not confuse or delay prompt disaster operations in the event we are attacked.
(Quesada 1951)

In terms of objective (treatment of early casualties), this is a logical statement. However, in view of the possible enormous escalation of effects from radioactive fallout later revealed by Operation Castle, it needs some caveats.

10. In Operation Ivy, a small team of biologists collected samples from seven major stations rimming the Eniwetok Atoll, some of them used in the surveys of 1948 and 1949. There were pretest samples of algae, fish, and invertebrates and rats collected in traps before the test shot "Mike." Afterward, collection teams gradually re-entered, but for the first time since Baker were constrained by residual radiation levels that threatened to exceed "the cumulative exposure limits prescribed by RadSafe" (Hines 1962, p. 141). The data immediately showed that the levels of activity in many of the samples were so high that large amounts of radionuclides could be expected in the biome. For example, the plankton tows that in earlier shots had contained relatively low levels of radioactivity were two to three hundred times higher in the post-Mike shot samples (Hines 1962, p. 147).
11. The highest concentrations of radionuclides appeared in omnivores, probably because they added surface contamination from plant foliage they ate to that ingested via meat, etc.
12. By 1953, six years after creation of the Pacific Proving Ground, a more or less permanent laboratory for biomedical work was established on Parry Island. This was during the period when John Bugher was director of the AEC Division of Biology and Medicine. In addition to the people from the Applied Fisheries Laboratory of the University of Washington, the laboratory also accommodated scientists from the AEC New York Operations Office, and others. It was called the "Eniwetok Marine Biological Laboratory."
13. The Mike shot added a new dimension to the worldwide fallout problem, viz., injection of contamination into the stratosphere.
14. Some of the differences in dimensions of the fallout problems to the marine environment as compared to the terrestrial were reinforced along the lines described in chapter 11.
15. An inescapable conclusion was that, although the thermonuclear device theoretically produced less inherent radioactivity per unit of yield, the much larger yield could entrain enormous amounts of debris, and the high neutron flux could produce very large quantities of activation products. Thus, except for a very high altitude burst, the problems of fallout did not go away by shifting from fission to fusion.

D. Operation Castle, Shot "Bravo"—The Roof Falls In

1. The Event

On March 1, 1954, an experimental thermonuclear device was exploded on Bikini Atoll in the Marshall Islands with results far different from those expected. First, the yield was well above expectations, and the part of the atoll on which the device was detonated essentially disappeared as a huge cloud of coral mixed with fission products, activation products, and other debris. Second, the carefully predicted winds blew from the right way at the surface but from the wrong way aloft. Because of the high altitude to which the debris was carried (over one hundred thousand feet) and lack of knowledge of the wind directions up there and a shift of wind nearer the surface just after the test, the fallout went south over inhabited atolls and on the ships of Joint Task Force Seven. Also, the cloud dropped fallout over thousands of square miles of open ocean, far beyond the range of thermal and blast effects. As we all know, some of it fell on the 99.9-ton Japanese fishing boat named *Fukuryu Maru No. 5* ("Lucky Dragon" in English).

The story has been told in detail in many places, ranging from official reports of both the United States and Japan, through symposia (e.g., Cohn, Robertson, and Conard 1960), a graphic description by Hines (1962, chapter 7), to the *Saturday Evening Post* (Sherrod 1954).

Eighty-two Marshallese were evacuated from Rongelap and Ailinginae Atolls and 154 from Utrik Atoll to Kwajalein and later to Majuro Atoll. The 82 from the closest island showed significant biological effects and required considerable attention, as we will see. Those from Utrik were returned to their homes after some months. The total of Marshallese persons receiving measurable levels of gamma exposure from fallout came to 239 (Cohn, Robertson, and Conard 1960). The exposures included both external radiation doses and beta doses from suspended and deposited fallout, plus inhalation and ingestion exposures (especially on Rongelap and Utrik).

During the early hours, preliminary care and evaluations of the exposed populations were initiated by the station medical officer, Commander W. S. Hall. As soon as possible, medical and scientific teams were brought out from various U.S. installations, especially the NRDL in San Francisco (see chapter 13); the Armed Forces Special Weapons Project; the AEC's Division of Biology and Medicine; and the Naval Medical Research Institute in Bethesda.^(a)

In addition to the medical care and follow-up, much was done to ascertain the condition of and radionuclide contents of plant and animal life exposed to the fallout. This was done partly for its intrinsic interest and partly as an aid in determining the probable exposures of the humans.

Despite the fact that the events of March 1, 1954, set the stage for a marked "intensification on an international scale of medical and biological investigations related to the problem of nuclear fallout" (Hines 1962, p. 178), early

(a) A sample of the frenetic conditions behind the scenes can be gleaned from a personal interview with Stanton Cohn (Cohn 1982). In 1954, he was on the staff of NRDL and had been doing experimental work with radionuclides. He received word late one night to be prepared to depart as soon as possible on a secret mission and to bring along equipment and drugs for potential use in decorporation of radioactive materials from humans (see chapter 19). As we will see, this led to Dr. Cohn's twenty-five-year association with the problems of the Marshallese.

announcements and information from Washington were terse and uninformative. It was March 11 before an announcement was made about transporting of residents out of the area, and it stated, "There were no burns" (AEC 1954). It was not until the *Fukuryu Maru No. 5* reached its home port of Yarusu, Japan, that the lid had to be lifted, but even then it was done somewhat reluctantly in matters of detail.^(a)

Reports began to appear gradually during the succeeding weeks, and scores of meetings soon involved most of the relevant scientific community. A fairly complete listing of individuals and institutions concerned, at early as well as later phases, is given in the first relatively complete and unclassified document on the subject, issued by the AEC in 1957 (Dunning 1957a). Most of those participating are already familiar to us from earlier chapters, but it is interesting to note that AEC Headquarters staff took active roles, along with those from NRDL, the Applied Fisheries Laboratory, UCLA, and others.

Before we consider further details of the biomedical work, it is of interest to ponder further upon the very large quantity and extent of the fallout from Shot "Bravo." True, the shot was at least 15 megatons in yield, and it was close to the surface on a tower. Millions of tons of the substratum were dislodged and became airborne. But these suspensions are characteristically of fairly large particle size and should return to earth more or less within the radius planned upon by the test organization. Was the pulverization unusually complete or was there another factor?

Ralph Lapp considers these questions in his book *Atoms and People* (Lapp 1956) and concludes that no calculation using ordinary assumptions could account for the quantity and extent of the fallout. He decided that the Bravo device had a skin of natural uranium, which could be made to fission by the very energetic neutrons of the fusion process. Thus, the hydrogen bomb could have an added component of ordinary fission products, and these could be carried considerable distances, especially since some of the precursor substances were gases. Lapp was convinced that these contributed considerably to the exposures at a distance, such as the Japanese fishermen. He had no access to the secret data regarding the bomb, but he did get copies of a scholarly publication by Japanese scientists analyzing the fallout dust. They had found ^{237}U on the deck of the *Lucky Dragon*. Uranium-237 is a normal product of bombardment of ^{238}U by very fast neutrons. The ^{237}U was not in sufficient quantity to be radiobiologically important, but it confirmed Lapp's calculations.

This instance is mentioned primarily to emphasize that measures can be taken to increase fallout activities greatly and produce a very "dirty" hydrogen bomb. Such measures could include the fissioning of a natural uranium shell as above, or of a cobalt shell that can produce a very highly radioactive fallout in great quantity.^(b)

(a) It is not appropriate in this research compendium to enter further into discussion of the pros and cons of dissemination of information, or the reasons for the guarded attitudes. It does seem clear that the Marshallese and Americans exposed received care as rapidly as possible, despite lack of public information. Whether or not more could have been done for the Japanese, both the fishermen and the general populace who worried about contaminated food, is for others to say. The problem seems to have been in part one of attitude, or perceived attitude.

(b) As we will see in connection with Project Plowshare, measures can also be taken to reduce fallout and make a "cleaner" bomb.

Thus, the March 1, 1954, shot showed not only what ordinary fallout could be like from a large detonation at surface level but also what special features could be incorporated and should be considered possible in any projections of fallout effects from other devices. Indeed, the H-bomb might be regarded as a gigantic A-bomb rather than "clean" (Lapp 1956).

Figure 12.4A shows the apparent contours of the lower altitude fallout doses integrated for a two-day period. In figure 12.4B, the doses at specific atolls are shown. (a)

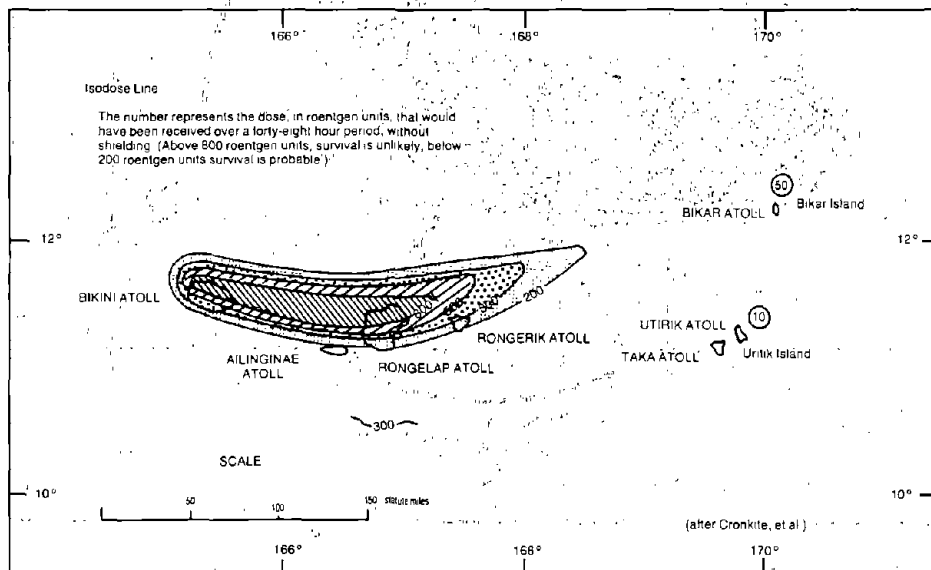


FIGURE 12.4A. General pattern of fallout from March 1, 1954, test at Bikini. (Modified slightly from Micronesia 1973.)

2. The Marshallese

The group of natives on the Marshall Islands accidentally exposed to the fallout from Shot "Bravo" required immediate medical examination and care. Also, they, with the twenty-six American military personnel who were on the island, represented the only population of human beings exposed to weapons-type fallout and, as such, they provided possible comparisons with the populations of the Japanese cities exposed to high doses of external radiation. Thus, the prospect of long-term care and study seemed very real. Although there were occasions when the patients wondered if all the fuss and repeated examinations was more for research than for them, (a) on the whole, the operation provided a unique mixture of needed medical care and the collection of important information.

(a) Indeed, examinations were suspended in summer 1960 to give them a breather and a chance to adjust to their return to their native island.

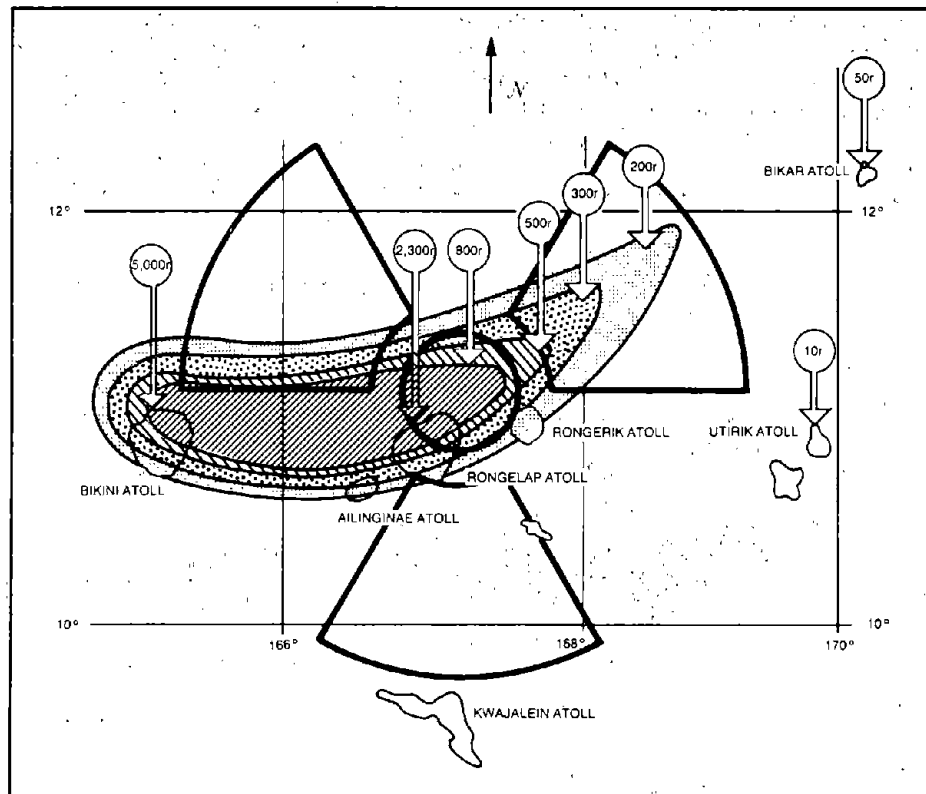


FIGURE 12.4B. More on radiation doses on individual atolls at the same time, approximately as the dose rate contours shown in figure 12.4A. (Modified slightly from Micronesia 1973.)

Early care was provided by the military and special-teams from laboratories such as the Naval Medical Research Institute, the NRDL, the Walter Reed Army Medical Research Center, and others. The first wave was directed by Dr. E. P. Cronkite. There was a resurvey at six months done under Dr. V. P. Bond, and another at twelve months done under Dr. Cronkite. Beginning in 1956, the center of operations shifted gradually to the Brookhaven National Laboratory (BNL) on Long Island, N.Y. This came about partly because some of the key physicians (e.g., Bond and Cronkite) moved from the NRDL and the Naval Medical Research Institute to Brookhaven, and partly because it became obvious that it would be a long-term operation. There thus began over a quarter century of continued work by the Medical Department at BNL, with numerous collaborators from other organizations (e.g., Case Western Reserve University; M. D. Anderson Hospital; University of Pittsburgh; National Institute of Health; Trust Territory of the Pacific Islands; Hiroshima University; National Institute of Radiological Sciences, Japan; U.S. Public Health Service; University College Hospital, London; U.S. Veterans Administration; etc.). The results appeared in a series of BNL reports and related publications that are listed, without the collaborators since there were too many, in the bibliography (Cronkite et al.

1955a,b; Conard et al. 1956, 1957, 1958, 1960, 1962, 1963, 1963-1964, 1967, 1970, 1975, 1980; and Conard 1977).^(a) Of these, the twenty-year review (Conard et al. 1975) is especially complete with background and history and is especially well illustrated.

The work is continuing, but with retirements of Conard and some of the other principals, the study has shifted largely to reconstruction of the dosimetry.^(b) This new work is being done largely in the former Health Physics Division, now Safety and Environmental Protection Division, at BNL, with reports already completed by Greenhouse and Miltenberger 1977; Greenhouse, Miltenberger, and Cua 1977; Greenhouse, Miltenberger, and Lessard 1979, 1980; Lessard, Greenhouse, and Miltenberger 1980; and Naidu et al. 1980.

While the work has been described in open literature publications and in the Congressional hearings cited earlier in this chapter, the BNL reports provide the most complete story. Generalized reviews were presented in AEC (1956), Dunning (1957a), Conard (1956, 1961) as well as in some of the journal publications cited.

It should be emphasized that the professional teams had a wide geographical and disciplinary base. There were medical observers from Japan and from the Congress of Micronesia, AEC observers, collaborators from the Atomic Bomb Casualty Commission (ABCC) in Hiroshima, and a cadre of medical and technical specialists from institutes throughout the United States and elsewhere.

The Congress of Micronesia developed a special joint committee and produced a report of its own under the Fifth Congress of Micronesia in February 1973 under the chairmanship of Senator Olympio T. Borja (Micronesia 1973). While the basic findings in this report coincide with those in the BNL and AEC reports, there are also some points of difference and an airing of some problems they felt were important and were not reflected fully in the American documents.

The basic sequence of findings and research progression is given in the following paragraphs:

1. In the first two days, some of the exposed people from Rongelap experienced anorexia, nausea, and vomiting. This was partly due to the gamma exposure and partly due to ingested material, estimated at about 3 mCi.^(c)

2. In about a week, beta burns began to show and were clearly evident by two weeks on the exposed flesh of the natives. There were marked variations depending upon location, whether or not they had bathed, etc. A typical example can be found in figure 12.5, which shows beta radiation lesions of the feet at four weeks after exposure and the sequence of healing.^(d) Interestingly, although some of the lesions, especially ones in folds of skin, became ulcerated, they remained relatively superficial. No skin cancer has yet been seen from any of these lesions.

(a) I am grateful to Dr. Conard for keeping me on his mailing list for many years and to Dr. Lessard for providing a complete set of these classic documents.

(b) The medical surveys are being continued under the direction of Dr. William Adams at BNL with collaborators.

(c) Fortunately, the material was relatively insoluble and passed through the gastrointestinal tract quickly. The gastrointestinal-tract symptoms lasted about two days and had largely disappeared by the time the people reached Kwajalein.

(d) Excellent color photographs can be seen in the AEC documents cited.



PLATE 5.—Hyperpigmented raised plaques and bullae on dorsum of feet and toes at 28 days. One lesion on left foot shows deeper involvement. Feet were painful at this time.



PLATE 6.—Lesions 10 days later: Bullae have broken, desquamation is essentially complete, and lesions have healed. Feet no longer painful.



PLATE 7.—Lesions 6 days later showing repigmentation except for small scar on dorsum of left foot at site of deepest lesion.

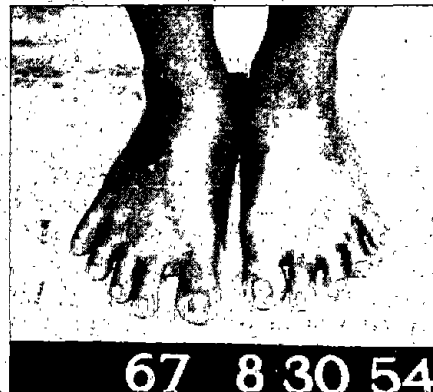


PLATE 8.—Same case as in Plate 5, six months later. Foot lesions have healed with repigmentation; except depigmented spots persist in small areas where deeper lesions were.

FIGURE 12.5. Beta radiation lesions of the feet four weeks after exposure and sequence of healing. (Photos from Conard et al. 1956.)

3. There were a few mild cases of epilation in the highest dose groups.
4. Blood counts were begun quite early. They showed significant lowering of leukocyte and platelet counts. This was most marked in the Rongelap people (estimated gamma dose, 175 rad) but was detectable in the Utrik people (estimated dose, 14 rad). The lymphocytes dropped to about half the normal level in adults and a quarter of the normal level in children under five years of age. Neutrophils fluctuated early but settled at about one-half the control level after five to six weeks. Of special interest is the slow recovery of the blood cell levels.

Only the neutrophils were back to normal at twelve months. It was not until the eleven- and twelve-year surveys that the hematological picture finally returned to levels comparable to those of the unexposed population of the area.

5. In later years, bone marrow samples were added occasionally for determination of possible chromosome aberrations. Some were found, but their significance could not be ascertained.

6. Considerable effort was expended to find the nature and extent of the contributions of radionuclide intake. This was accomplished early by the collection of urine samples. Later, the survey teams brought equipment from BNL for whole-body and organ counting. This included first a makeshift steel room and later arrangements of lead bricks as shown in figure 12.6.A and B.^(a) No measurements showed body or organ burdens of any radionuclide more than a small fraction of the maximum permissible burden. However, there was definite evidence even from the early urine samples that radionuclides had been deposited in the body. While it was clear that these deposits did not contribute much to the early doses, their persistence in the body and in the environment could obviously add up to potentially significant doses over the years.



FIGURE 12.6A. Steel room used for whole-body gamma spectroscopy on the Marshall Islands. It resided on Kwajalein between surveys. (Photo taken from Conard et al. 1975.)

(a) The steel room and other heavy equipment remained on the atoll. However, the electronics were too subject to the effects of humidity, heat, and sand to be left there; they had to be transported back and forth for each survey. Stanton Cohn tells of a harrowing incident on the return trip from the first whole-body survey. The plane (military) developed engine trouble over the Pacific, and much expensive counting equipment had to be jettisoned to lighten the load. Also in their zeal to keep airborne, the crew jettisoned all of the data, originals that were waiting to be reproduced on return to the mainland and of which there were no copies (Cohn, 1983).

FIGURE 12.6B. Arrangement of lead bricks used for whole-body counting. This replaced the steel room and was made possible by improved electronics. (Photo taken from Conard et al. 1975.)



The estimated early body burdens of several radionuclides in the Rongelap people are given in table 12.1. Note that the early activity for ^{131}I in the thyroid is the highest, with ^{89}Sr (not ^{90}Sr) in second place, and that cesium is not even mentioned. For comparison, figures for 1970–1974 for several isotopes in individuals from three islands are shown in table 12.2. Note that the activities in urine do not vary much from year to year and that ^{137}Cs in this period greatly exceeds the amount of ^{90}Sr . Such results indicate that the radioisotope contents are being continually replenished from the environment. Almost none could be left, except perhaps a little strontium in bone, from the original depositions. The gamma spectra from the whole-body counting showed a pronounced peak at the ^{137}Cs energy level in the Rongelap subjects, much less in members of the BNL medical team. The quantities were in the range of a few nanocuries per kilogram body weight.

TABLE 12.1. Estimated Body Burden (μCi) of Rongelap People

	Activity at 1 day	Activity at day 82
^{89}Sr	1.6 - 2.2	0.19
^{140}Ba	0.34 - 2.7	0.021
Rare earth group	0 - 1.2	0.03
^{131}I (in thyroid gland)	6.4 - 11.2	0.0
^{103}Ru	0 - 0.013	—
^{45}Ca	0 - 0.019	0.0
Fissile material	0 - 0.016 (μg)	0.0

Source: Reset from Conard et al. 1975.

7. A few bone samples were obtained from autopsies of individuals dying from causes that were, with one exception, not related to radiation. The ^{90}Sr found in these bones gave calculated body burdens that agreed well with those calculated from urinalysis.

TABLE 12.2. Radiochemical Analyses of Urine (Data in Average pCi/liter)

Year	No. in group	Av. vol., ml	Av. Ca, mg/liter	⁹⁰ Sr	¹³⁷ Cs	²³⁸ Pu	²³⁹ Pu	^{239,240} Pu
Rongelap								
1970	20	895	152.4	3.5	2700			
1971	15	534	336.1	3.7	2400			
1972	18	461	120.3	2.4	2600			
1973	11	249	247.2	6.5	4600			0.21
1974	14	558	706.8	2.8	4500			
Utirik								
1974	11	542	734.9	1.3	1300			
Bikini								
1970	Pooled		120.0	1.2	115	0.003	0.003	
	Urine C	1100		2.2		0.013	0.020	
	Urine M	930		1.9		0.015	0.024	
	HASL* control	3000	160.0	1.0	12	0.003	0.003	
	HASL control	1000		1.6		0.014	0.022	
1971	Pooled	2670	84.5	1.7	183			0.004
1972	Pooled	2700	204.0	4.2	910			
1973	14	294	173.5	6.7	1500			
1974	11	141	310.0	2.0	1100			0.02
(Spring)								

* US AEC Health and Safety Laboratory, New York, N.Y.

Source: Reset from Conard et al. 1975.

8. There was no question but the burdens of several radioisotopes began to climb soon after the return of the population to Rongelap in 1957. The contents of strontium and zirconium (from eating fish primarily) peaked at about 1960-1963 on Rongelap, but the ¹³⁷Cs burdens held high much longer. Indeed, it is ¹³⁷Cs in the soil that is one of the current concerns about the Bikinians and that resulted in their being taken off their island again. (A few had been repatriated.)

9. One source of continuing replenishment of the body burden of ¹³⁷Cs and of ⁹⁰Sr is the coconut crab. This large creature, capable of puncturing a coconut and long a staple in the diet of the Marshallese, has been measured regularly and found to be consistently high in both ⁹⁰Sr and ¹³⁷Cs. Some typical data are shown in table 12.3.

Despite warnings not to eat the coconuts or any other produce from the local soil,^(a) the Marshallese could not resist (or possibly they did not understand fully the reasons for the prohibitions). They were undernourished. Coconut crabs were a great delicacy, especially when the alternative was C rations. While the local fish were gradually decreasing in radioactivity, and thus the intake of isotopes like ⁶⁵Zn from them was constantly reduced, the land-bound animals

(a) Extensive gardening was attempted to help reduce dependence on imported foods and to make the islanders' life style more nearly normal. This did not work. The crops picked up too much radioactivity from the soil.

TABLE 12.3. Radionuclides in Coconut Crabs from Rongelap

Year	¹³⁷ Cs, pCi/kg	⁹⁰ Sr, pCi/g Ca
1961		1,140
1962		1,224 (1,317; 1,086; 1,113; 1,378)
1964	50,281 (39,292; 45,318; 66,234)	758 (865; 628; 780)
1965	12,700	724
1969	7,775 (8,540; 7,010)	705 (910; 500)
1972	5,900 (5,600; 6,100; 6,800; 5,100)	353 (376; 419; 359; 259)
	12,900*	933*
1973	37,065 (64,700; 9,430)*	3,950 (6,639; 1,267)*
1974	6,600 (5,000; 8,200)	448 (290; 606)
	4,800*	290*

* From northern islands of Rongelap Atoll, where radiation dose was much higher.

Source: Reset from Conard et al. 1975.

and plants could and did act as a large reservoir for maintaining significant levels of radioactivity in the population, a largely unexpected result.

10. A large number of other health determinations were made and showed essentially no effect of the exposure over the first decade. These included general health, disease resistance, nutrition, growth and fertility, and incidence of cancer. Indeed, there was a fairly prolonged "silent period" after the initial effects had cleared.

11. By the time of the nine- and ten-year surveys, changes in the thyroid gland began to appear. Three exposed teen-age girls showed thyroid nodules. Three more cases appeared in the eleven-year survey, two in boys twelve to seventeen years of age, and one in an adult woman of forty-one years. By the twelfth year, there were eighteen cases of thyroid dysfunction, sixteen with nodules, and two with hypothyroidism. At later times, effects could be seen as growth retardation, particularly in some of the boys. This was reversed by treatment with thyroid hormone started in September 1965. Reviews have been published by Conard et al. (1969), Larsen et al. (1978), and others. The picture in March 1969 is shown in table 12.4. Typical calculations of dose along with data on incidence by December 1974 are shown in table 12.5. It appears that the early calculations failed to consider the possibility of a much larger dose to the thyroids of children because of the small size of the thyroid in the child.

As might be expected, these findings led to much emphasis on thyroid and thyroid-related effects in all of the subsequent work. Some of the patients were flown to the United States for more careful measurement of their body and organ burdens, first at Argonne National Laboratory (ANL) where C. E. Miller had just set up whole-body counting (chapter 18), later at BNL. Some were brought over for thyroid surgery in New York, Boston, and elsewhere.^(a)

(a) A question has been raised regarding the seriousness of some of the cases since a handsome sum was paid by the U.S. government to individuals requiring thyroid surgery. Medical supervision was competent, honest, and tight and allowed little chance for maligning.

TABLE 12.4. Thyroid Nodules (Plus Hypothyroidism), March 1969

Group	Age at Exposure	Estimated Thyroid Dose, ^a rads	Percent Thyroid Lesions ^b	Percent Malignancy ^b
Rongelap (175 rads γ)	<10	500-1400	89.5 (17/19)	5.3 (1/19)
	>10	160 ^c	8.8 (3/34)	5.9 (2/34)
	all	—	39.6 (21/53)	5.7 (3/53)
Ailingnae (69 rads γ)	<10	275-550	0.0 (0/6)	—
	>10	55	12.5 (1/8)	—
	all	—	7.1 (1/14)	—
Utrik (14 rads γ)	<10	55-110	0.0 (0/40)	—
	>10	14	5.1 (3/59)	1.7 (1/59)
	all	—	3.0 (3/99)	1.0 (1/99)
Rongelap unexposed	<10	—	0.0 (0/61)	—
	>10	—	2.3 (3/133)	—
	all	—	1.5 (3/194)	—

^a Dose from ¹³¹I, ¹³²I, ¹³³I, ¹³⁵I.^b Based on present population.^c Children 10 to 20 years of age at exposure received up to about 500 rads.

Source: Modified slightly and reset from Conard et al. 1970.

The growth retardation was greatest in those receiving the dose at the early critical stages of growth. Thus, there were cases of the older of two siblings (both boys) being considerably shorter than the younger. After eight years of thyroid hormone therapy, the two boys were of nearly equal height. These are pictured by Conard et al. (1975) and in AEC publications.

Much additional work that was done to assess thyroid function cannot be reviewed here. Suffice it to say that ample details appear in the BNL reports, and they include biochemistry and histology in extenso.

Fortunately, it appears that no one proceeded to fatal thyroid neoplasia, but thyroid cancer did occur; the results raised questions about our knowledge of the sensitivity of the human thyroid. The calculated radiation doses, particularly in adults, were lower than those expected based on general clinical findings and animal experiments (chapter 8) to be associated with such a high incidence of effects (nodules). Are the Marshallese especially sensitive, or was there some mistake in the dosage estimation? Were the total doses actually higher than those calculated from the measurements of fallout and urinary excretion? A significant portion of the BNL work is now directed toward reviewing and reanalyzing all information to double-check the doses and to obtain whatever new data are possible.

The re-evaluation involves the pooled urine analysis data in the light of current retention models, reestimation of airborne concentration of radioiodines on the basis of neutron irradiation of ¹²⁹I deposited in the soil, manipulation of meteorological models, and reanalyses of Bravo debris. There was a BNL report reconstructing the possible chronic doses at Rongelap and Utrik (Lessard, Greenhouse, and Miltenberger 1980) and one on internal exposure to the Marshall Islands residents from ¹³⁷Cs, ⁶⁵Zn, ⁹⁰Sr, ⁵⁵Fe, and ²³⁹Pu (Lessard,

TABLE 12.5. Thyroid Lesions in Marshallese, December 1974

Group	Age at Exposure	Est. Thyroid Dose, ^a rads	% Subjects ^b with Thyroid Lesions	No. Subjects with Surgery	% Subjects ^b with Malignant Lesions
Rongelap exposed (175 rads)*	<10	810-1150	89.5 (17/19)	15	5.3 (1/19)
	10-18 ^c	335-810	16.6 (2/12)	1	
	>18	335	9.1 (3/33) ^d	3	6.1 (2/33)
	All	556 ^e	34.4 (22/64)	19	4.7 (3/64)
Ailingnae exposed (69 rads)*	<10	275-450	33.3 (2/6)	1 ^f	
	10-18	190	0.0 (0/1)	0	
	>18	135	36.3 (4/11)	3	
	All	217 ^e	33.3 (6/18)	4	
<i>In utero</i> exposed		175+?	33.3 (1/3)	1	
		69+?	0.0 (0/1)	0	
Utrik exposed (14 rads)*	<10	60-95 ^g	0.0 (0/58)	0	
	10-18	27-60	4.8 (1/21)	1	4.8 (1/21)
	>18	27	6.4 (5/78)	3	
	All	50 ^e	3.8 (6/157)	4	0.6 (1/157)
Rongelap unexposed	<10		1.6 (1/61)	0	
	10-18		7.7 (1/13)	1	
	>18		5.8 (7/120)	2	
	All		4.6 (9/194)	3	
Likiep unexposed	<10		0.0 (0/31)	0	
	>10		4.7 (5/106)	0	
	All		3.6 (5/137)	0	

^a Dose from ¹³¹I, ¹³²I, ¹³³I, and ¹³⁵I plus gamma; mean dose extrapolated from calculations for adults and 3-year-olds.

^b Based on number of people exposed, excluding those *in utero* (number of cases/total number in group).

^c The thyroid is considered to be fully developed by about age 18.

^d One additional case of adenoma; found at autopsy, not included here.

^e Weighted mean dose.

^f Pathologists differed as to whether this lesion was malignant; it was scored as benign.

^g The more energetic, shorter-lived isotopes of iodine contributed less to the total thyroid dose in the Utrik people because the fallout occurred later there. It might be surmised also that the biological effectiveness of the thyroid dose per rad would be less in the Utrik group.

*External dose.

Source: Modified slightly from Conard et al. 1975.

Miltenberger, and Cohn 1980). Dose contributions from these during the rehabilitation period exceeded the external dose equivalent received during that time but did not contribute significantly to the thyroid dose. There is also a large report in draft stage on bioassay and dose assessment for Bikini Island residents (Miltenberger et al. 1983) that we will await eagerly. (See preliminary publication by Greenhouse, Miltenberger, and Lessard 1980.)

Although the above comprehensive analysis of the exposures from all important radionuclides is still being compiled, the Brookhaven group issued a complete reconstruction of the thyroid dose. Lessard et al. (1985) concluded that the mean population thyroid doses received on March 1, 1954, were

2,100 rad (21 Gy) at Rongelap, 670 rad (6.7 Gy) at Sifo, and 280 rad (2.8 Gy) at Utrik. These increased dosage estimates brought the corresponding risk figures much closer to those estimated from the populations exposed at Hiroshima and Nagasaki and other estimates of thyroid-risk in humans. They put to rest, in a general way, the nagging inconsistencies that had persisted concerning the thyroid effects seen and the earlier estimated doses. They also concluded that ingestion was the primary route of entry.

A major contribution to the increased estimate of total dose appeared to be inclusion of all of the radioiodines and tellurium, rather than ^{131}I alone. Thus, the total from these was 7.7 times the absorbed dose from ^{131}I at Rongelap, 10 times at Sifo Island, and 4.7 times at Utrik Island. Bioassay results for ^{131}I seemed to be reasonably reliable if these factors were considered, but some other approaches, such as the use of ^{129}I , did not contribute as much as had been hoped. Thus, after thirty years, which included over a decade of work on the dosimetry, the medical observations and dosage reconstructions have been brought into reasonable agreement, a considerable feat in view of the complexities involved.

Open literature publications bearing on the dosimetric aspects and modeling have also appeared; see, for example, Lessard, Miltenberger, and Greenhouse (1980) on dietary radioactivity intake by the Bikini Island residents; Greenhouse, Miltenberger, and Lessard (1980) on the dosimetry in general; and Miltenberger, Greenhouse, and Lessard (1980) on whole-body counting results.

12. We mentioned that no excess malignancies, except for thyroid neoplasias, appeared in the earlier surveys, and even the thyroid cases appeared quite late in the total survey period. In 1972, an exposed Rongelap male died of leukemia at age nineteen at the National Institutes of Health (NIH) Clinical Center in Bethesda, Maryland, where he had been brought for urgent treatment. He had received 175 rad of gamma radiation at age one and had showed the early transient gastrointestinal symptoms. At age thirteen, he had developed thyroid nodules and was one of those taken to the United States for study and surgery of benign nodules. Review of the hematological and other data supported the possibility that this leukemia was associated with radiation exposure.

Despite the tentative nature of the evidence for causation, this case caused a considerable stir. It was decided immediately to do complete hematological examinations of the exposed Marshallese every six instead of every twelve months. The Micronesian Congress paid considerable attention to the development, possibly because leukemia is relatively rare in that population.

There was a slightly increased incidence of other cancers in the exposed Rongelap people at later times, but it could not be correlated with radiation exposure because of the smallness of the group, uncertainties in diagnosis, and the fact that the malignancies were not like those connected with radiation exposure of the Japanese as determined by the ABCC.

The care and study of the Marshallese is still continuing. One of the thorniest problems has been final repatriation of the entire population and the question of whether or not many islands should be scraped to reduce contamination, as was done for some. The body burdens of radionuclides of individuals that moved back to Bikini showed alarming tendencies to rise with time. Some of those on other atolls rose also, but to a lesser degree.

These phenomena may have meant primarily that the fairly rigid dietary prohibitions were not being observed. Or perhaps there were some miscalculations in the potential biological availability of the contaminants in the soils. The

debate is still continuing, and the research efforts being applied are largely extensions of what we have already reviewed:

The continuing rise of ^{137}Cs in the residents led to their re-removal from the area in 1978. This was not only a bitter reverse for these happy people, but a somber indication of how far into the future the consequences of fallout contamination may extend, this time largely through gardening in contaminated soil.

Unfortunately, the age of contention and litigation has reached even to the Marshall Islands. There are now more biopolitical problems than scientific. Each exposed native has received a generous financial settlement from the U.S. government, but this is considered no substitute for being able to return to one's homeland. The process has occupied more and more attention in the Department of Energy Headquarters (Deal 1979, 1980), and several large "in-house" reports deal extensively with these problems (e.g., AEC 1974; Bair et al. 1977; Clusen 1980; Kohn and Dreyer 1982). There was in addition a Bikini Atoll Rehabilitation Committee that operated under the Department of Interior. Its first report was submitted to the U.S. Congress, House and Senate Committees on Interim Appropriations (BARC 1984, 1985). This report concludes that the hazards of resettlement of Bikini Atoll stem almost entirely from the presence of ^{137}Cs . Strontium-90 plays only a minor role, and plutonium is not mentioned. It also concludes that Bikini could be resettled now and meet federal radiation protection standards, but only if no foods were grown or ground water consumed for a period of eighty years. Eneu could be resettled and meet federal radiation protection standards if a portion of the needed food, depending on population size, were imported. This solution was not acceptable to the Bikini-Kili Council, who want the sites decontaminated. The Committee is now working on potential plans for attacking the problems directly (e.g., "removing the top 30 cm of Bikini's soil") and needed pilot studies. The committee was chaired by Henry I. Kohn, professor of radiation biology emeritus, Harvard Medical School. He was assisted by A. S. Kubo, BDM Corporation; F. L. Petersen, University of Hawaii; and E. L. Stone, professor emeritus, Cornell University. (a)

A considerable effort has been made to present full discourses to the Marshallese on the exact meaning of the radiation on the atolls and the reasons for the various decisions made. These books were prepared for the Department of Energy by William J. Bair, Battelle, Pacific Northwest Laboratories; John W. Healy, Los Alamos National Laboratory; and Bruce W. Wachholz, Office of Environment, Safety and Health, U.S. Department of Energy (Bair, Healy, and Wachholz 1979, 1980, 1982) in what must be characterized as purely a labor of love. They were joined in close collaboration by translators, Alice Buck, Honolulu, Hawaii; and Meleran-Jelke and Kiorong Sam, Republic of the Marshall Islands, Trust Territory of the Pacific Islands. Technical editor was Ray Baalman, Battelle, Pacific Northwest Laboratories. The dose estimates were supplied by W. L. Robinson and colleagues at Lawrence Livermore Laboratory.

These three books, covering different atolls, are printed in both Marshallese and English on facing pages and are profusely and beautifully illustrated. As a

(a) Note added in proof: The June 1986 issue of *National Geographic* magazine contains a review of the problems of the Bikini natives (Ellis 1986). Unfortunately, it is a very incomplete review in that it concentrates only on very recent work and omits much of the enormous effort summarized in this chapter. Dr. Conard is pictured but not identified. There can be no argument, however, with Ellis's basic conclusions.

nontechnical account of all that went on of pertinence to the situation of the Marshallese, these discourses could, with amplification and generalization, serve as important primers to the general public on the subject of environmental contamination by radioactivity from fallout.

Despite all of these efforts, a referendum is about to be held to determine whether or not to sue the U.S. government and to find ways for the Marshall Islands to become independent of the United States. Resentment runs deep, and it resides in part in misunderstanding despite everyone's best efforts (see, for example, Appendix I to the review by Conard et al. [1975].)

With or without suits, we must conclude that the Bravo shot and its sequelae changed many views about fallout. About seven thousand square miles of territory downwind from the point of detonation were contaminated to the point that survival might have had to depend upon prompt evacuation or upon taking appropriate substantial shelter. (AEC 1955) had the areas been populated rather than largely open ocean. Also, while it should have been clear from the results of the first megaton-size bursts two years before, these events laid to rest permanently the idea that such very large explosions would eject the debris out of the earth's gravitational field, an idea considered seriously by some. The rest is more appropriately held for our discussion of worldwide fallout.

3. The Lucky Dragon and Sequelae

a. The Events

The exposure of the Japanese fisherman on the *Fukuryu Maru* No. 5 (*Lucky Dragon*) did as much, if not more, to bring fallout problems front and center on the world scene as the exposures of the populations on the atolls of the Pacific. Even though the *Fukuryu Maru* was moderately close to the announced danger zone, it was not actually inside of it, i.e., the calculated danger zone prior to the test. Unfortunately, the ship constituted such a small speck on the vast areas of open water that the reconnaissance planes missed it on their sweeps prior to the test. Also unfortunately, for reasons embedded in the strong relationships between Japanese workers and their employers, the ship never broke radio silence to ask what was happening, even though they saw the flash of the detonation.^(a) Instead, the ship plodded back to Japan with the twenty-two fishermen receiving daily doses from the accumulated fallout on the decks and their bodies and taking no special precautions to protect themselves or their catch of fish. The uproar began soon after the arrival of twenty-two sick fishermen at their home port of Yazu on March 17, 1954. This was soon viewed as crass disregard of Japanese interests on the part of the U.S. government, and it revived many of the only partially submerged emotions from Hiroshima and Nagasaki. Besides the sick fishermen, much concern focused on contamination of seafood, especially tuna. Many Japanese fish markets closed altogether. Fishermen were thrown out of work. A nation dependent on the sea for a substantial part of its food supply developed what was referred to in the press as "a great worry."^(b)

(a) Details of the many sociopolitical aspects of the incident are available in much of the literature already cited. A very graphic description can be found in Hines (1962), also Sherrod (1954), and the Congressional hearings already cited.

(b) It will soon be apparent that the Japanese did much more than worry.

True, there was a delegation sent from Washington, and the ABCC in Hiroshima offered full assistance. But there was an atmosphere of mistrust in the population verging on violence. Merrill Eisenbud (then head of the AEC Health and Safety Laboratory in New York, which had primary responsibilities for monitoring fallout) was one of the first Americans to reach Japan after the incident. When he arrived, he was met by an angry mob and for a while feared for his life (Eisenbud 1979).^(a) However, cooler heads prevailed, and, while there was need for much diplomacy on both sides, the Japanese dedication to good science predominated, and work began immediately to characterize and quantitate the situation. The Japanese did some excellent scientific work both in identifying the radionuclides in the residual fallout on the *Fukuryu Maru* and in monitoring the tuna and other seafood as it entered Japanese ports. Ultimately, over a million pounds of fish from about a thousand boats were tested. Of these, about 4% to 5% were found to be over limits and were buried or thrown into the sea.

Pictures of the *Lucky Dragon*, of some Japanese monitoring tuna, and a sign at a Japanese fish market are shown in figure 12.7A, B, C, D.

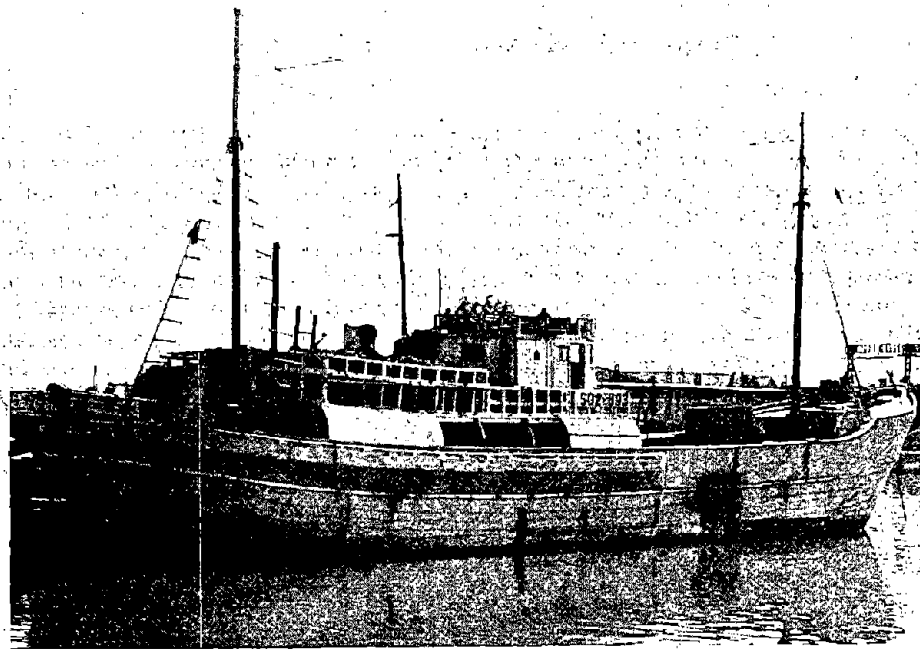


FIGURE 12.7A. The *Fukuryu Maru* No. 5 during her period of quarantine. (Reprinted from Hines 1962 with permission of University of Washington Press, Seattle, Washington, copyright 1962.)

(a) He was soon joined by Lauren Donaldson from the University of Washington and W. R. Boss from AEC.



FIGURE 12.7B & C. (Above and Right) Radiation survey of tuna conducted by Tokyo Metropolitan health authorities at the Tokyo Central Fish Market, 1954 (Sanitary Examination Laboratory, Tokyo). (Reprinted from Hines 1962 with permission of University of Washington Press, Seattle, Washington, copyright 1962.)

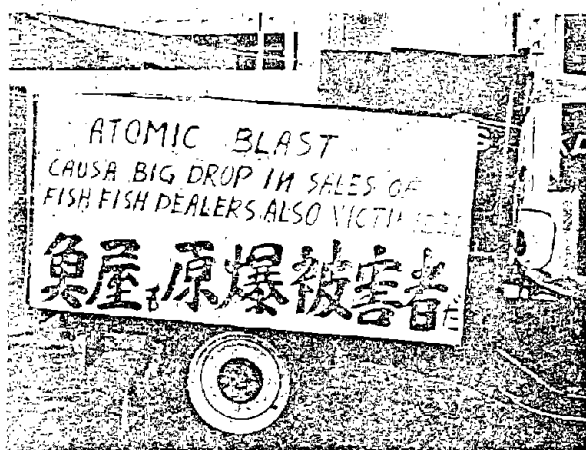


FIGURE 12.7D. (Left) Sign at fish market in Japan, March 1954. (Courtesy of Eisenbud 1976.)

The permissible radioactivity level was set at one hundred counts per minute measured on a beta-detecting Geiger-Müller counter at 10 cm from the body of the fish. This was considered a temporary "urgent" standard (Hines 1962, p. 175). However, except for possible hot spots, it probably provided sufficient protection from any health effects except the psychological trauma of eating fish with even one count per minute of what the Japanese called "Bikini ash." Incidentally, the distribution was very spotty. As Eisenbud (1976) described, one could monitor one hundred fish and find nothing, only to find a hot spot on the one hundred and first.

The medical care and eventual outcome of the sick fishermen were more complex. The physicians from the ABCC tried to help out, but there were many jurisdictional and professional problems.^(a)

This author has found few estimates of the total dose the fishermen might have received in their seventeen-day ordeal. Eisenbud made one in an oral presentation that this author was privileged to hear and of which he has a recording (Eisenbud 1976). Eisenbud's guess was a deposition of as much as 30 Ci/m² on the boat and an accumulated dose of up to 1,000 rad of beta-gamma and beta radiations. Japanese estimates were on the order of 500 to 600 rad (Suzuki 1956 and undated). No wonder the fishermen were sick!

In a sense, the ultimate effect of the *Lucky Dragon* incident plus the contamination of the Marshall Islands area was a watershed in the history of attitudes regarding the importance of fallout and the consequences of nuclear warfare. Even though the distribution might still have been regarded as "local" in contradistinction to "worldwide" (section VI), the potential areas and doses entered an entirely new category of significance. (Seven thousand square miles at dangerous levels of radioactivity is a substantial area!)

As cooperation between Japanese and American scientists became easier, several meetings and conferences were held. These have been described as increasingly cordial and informative, especially when the Japanese became convinced that the U.S. scientists were keenly interested in sharing all possible knowledge with them, and as it became apparent that the data being shared from the two sources were in basic agreement. Perhaps the area of most consistent agreement was on the activities and composition of the fallout and the activities in seafood. Since the Japanese had no access to data on the bomb itself, they went ahead on their own and constructed a very accurate picture of what had gone on. Dr. Kenjiro Kimura, a noted Japanese radiochemist and dean of the Faculty of Science at the University of Tokyo, and colleagues^(b) elsewhere worked out not only the basic story but even the presence of ²³⁷Np and ²³⁷U. The latter of these confirmed the calculations of Ralph Lapp as mentioned earlier. Also, Japanese scientists worked out the contents of the contaminated fish in detail (e.g., Dr. Toshihara Kawabata of the National Institute of Health, and others; see Hines 1962, chapters 7 and 8). Figure 12.8A shows Dr. Kimura at a ceremony where some of the radiochemical findings were announced. Figure 12.8B shows one of the early meetings of American representatives with the Japanese.

Meanwhile, back in Washington, the Joint Committee on Atomic Energy of the Congress held urgent hearings and special meetings. There was much controversy and acrimonious debate over the biological significance of fallout. A picture of one such meeting is shown as figure 12.9.

(a) There seems to have been much difference of medical opinion about some of the findings in these patients, including the question as to whether the one death from hepatitis resulted from the radiation exposure or a transfusion problem. All of the patients had drastically lowered white cell counts and followed clinical courses somewhat similar to those of the Marshallese, except that their blood cell counts seem to have returned to normal sooner (Kumatori 1975).

(b) The extent of the Japanese research effort can be found in a document entitled *Annex to Research in the Effects and Influences of the Nuclear Bomb Explosions* (Japan Society for Promotion of Science 1956). There were six major committees: for physics and chemistry (chaired by Dr. Kimura); for biology (chaired by Y. Okada); for medicine (chaired by R. Kobayashi); and for fisheries (chaired by Y. Okada).

FIGURE 12.8A. (Right) Dr. Kenjiro Kimura, noted radiochemist, at conference discussing Japanese findings. They had analyzed the "Bikini ashes" and had described the nature of the reactions involved within three days after the return of the *Lucky Dragon*. (Courtesy of Eisenbud 1976.) Note: Other Japanese scientists participating in the work and the arrangements are detailed by Hines 1962, chapter 7, p. 189 et seq.



FIGURE 12.8B. Early meeting of American representatives with Japanese concerning the exposed fishermen. Foreground, at right, Dr. John Morton, Medical Director of the Atomic Bomb Casualty Commission (on leave from the Chair of Surgery at the University of Rochester) and third on the right Merrill Eisenbud, Director of AEC's Health and Safety Laboratory. (Courtesy of Eisenbud 1976.) Identification of the others has not been practical.



FIGURE 12.9. One of several meetings of American scientists called by the Joint Committee on Atomic Energy of the U.S. Congress to discuss the biomedical significance of fallout. They are, from left to right, J. L. Kulp, Columbia University; W. F. Neuman, University of Rochester; Lt. Col. Hartgering, Walter Reed; W. H. Langham, Los Alamos; and Merrill Eisenbud, AEC Health and Safety Laboratory. (Courtesy of Eisenbud 1976.)

This last picture is shown partly because it involved some people whose work we have met elsewhere in this book and partly because it was these meetings that led to Cabot Lodge's request to the United Nations General Assembly that resulted in the founding of the United Nations Scientific Committee on the Effects of Atomic Radiation, UNSCEAR (Eisenbud 1976).^(a) All individuals in the picture agreed that definite and immediate limitations on nuclear explosions were necessary.

b. The Sequelae

The *Lucky Dragon* incident brought, among other things, urgent demands for determination of the extent and movement of radioactivity in the Pacific Ocean and the role played by living organisms. The Japanese were fearful that the contamination would move inexorably to their shores, contaminating their best fishing grounds on the way and even deny them the use of their beaches. Several expeditions were commissioned over the next few years to sample the waters and the organisms (see Hines 1962, chapters 7 and 8). These included:

1. A Japanese expedition that got under way on May 15, 1954, which used the *Shunkotsu Maru* and sampled over nine hundred thousand square statute miles of the Pacific.
2. A cruise by the *Keiten Maru*, a ship from the Faculty of Fisheries of Kogashima University between October 28, 1954, and January 28, 1955. It cruised largely in the Coral Sea.

(a) UNSCEAR has continued and represents an important source of authoritative and balanced information from international sources.

3. Three representatives of the Nankai Regional Fisheries Laboratory who made radiological samplings on a regular fishing cruise to the Fiji Islands between November 30, 1954, and February 19, 1955.
4. Operation Troll, a U.S.-sponsored project involving the Office of Naval Research, the AEC, the Scripps Institution of Oceanography, and others, with advisors or participants from every marine science laboratory in the United States. This was a fairly leisurely enterprise compared to the urgency of the Japanese cruises. It utilized the Coast Guard cutter, *Roger B. Taney*, and started its first survey on February 25, 1955. It did not return until May 3 after covering over seventeen thousand statute miles.
5. A cruise starting in June 1956 during Operation Redwing that utilized the destroyer escort, *USS Walton (DE-367)*. This ship was converted extensively to assist sample-taking and continuous monitoring of the activity in the surrounding sea water. Its survey area finally covered seventy-eight thousand square miles.
6. A cruise by the *USS Marsh (DE-699)* that followed up any contamination added by the shots of Operation Redwing.^(a)
7. As part of the "Operation Hardtack-Phase I" series in the Pacific in 1958, three sea surveys were involved. The first used the *USS Rehoboth (AGS-50)*, a seaplane tender converted by the Navy for oceanographic work. Later, with all the equipment transferred over from the *Rehoboth*, the *USS Collett (DD-730)*, a destroyer, was brought into service for surveys in the Central Pacific. Finally, after conclusion of the Pacific tests, a westward survey was done by the *USS Silverstein (DE-534)* (Hines 1962, p. 275).

There were underwater shots in the Hardtack Series, e.g., test "Wahoo," which involved a detonation at a depth of five hundred feet in May 1958. A primary purpose of the survey of the *Rehoboth* was to map out the spread of contamination from the underwater shot at the surface and at various depths. It could also add greater sophistication to the radioisotope determinations since there was a gamma spectrometer aboard the *Rehoboth*. A second underwater shot, test "Umbrella," detonated on the floor of the Enewetak Lagoon on June 8, 1958, involved the *Collett* in August. In September, the more wide-ranging cruise of the *Silverstein* took place. All of these involved sampling of biota as well as water, but only the *Silverstein* survey could be regarded as having the same long-distance objectives as the sea surveys operated shortly after the *Lucky Dragon* incident.

8. In addition to these extensive cruises, there were frequent surveys of the "local" waters of the Marshall Islands, as well as many terrestrial surveys by shore parties visiting the islands. Much of the former was done by people from the University of Washington and the latter by people like Frank Lowman, temporarily assigned to the Eniwetok Marine Biological Laboratory.

We can report a few of the results of these enormous undertakings:

1. The westward movement of the contamination stopped well short of the shores of Japan, deflected apparently by strong currents parallel to the Japanese coast.

(a) Maps of each of these cruises are given by Hines 1962, chapter 8.

2. Activity was easily measurable as far west as Guam, 1,200 mi west of Enewetak, but was only slightly above background at Palau, 1,950 mi west of Enewetak. It was not detectable in the Gulf of Siam, 4,250 mi from Enewetak. These phenomena are shown graphically in figure 12.10. Even more extensive measurements, some of them part of Operation Troll, showed radioactivity as far away as the Philippines, but still nothing in Japanese waters.

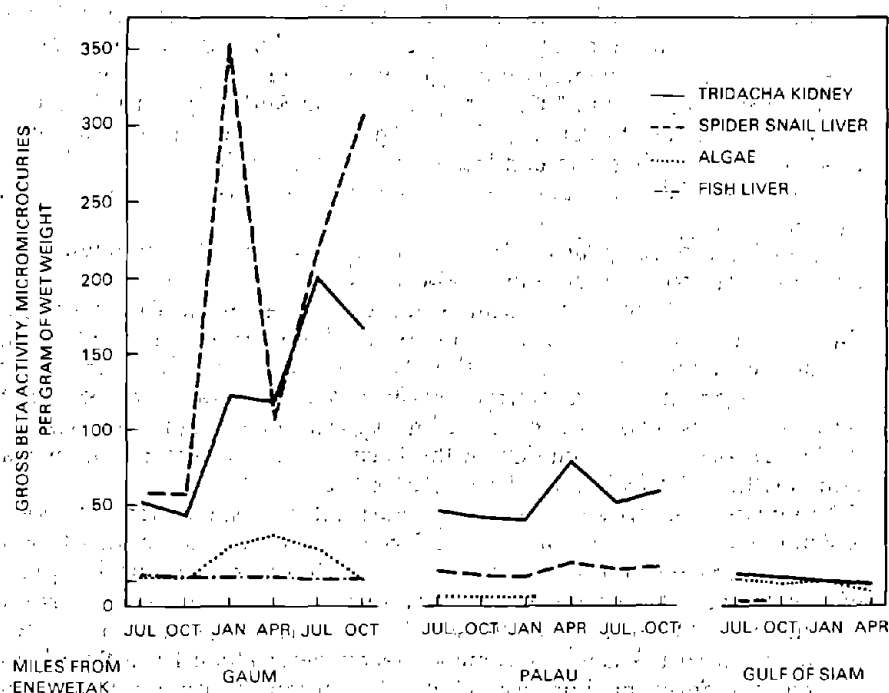


FIGURE 12.10. Average gross beta activity of marine organisms from Guam, Palau, and the Gulf of Siam, 1958–1959. Average based on two to thirteen observations. The original contained data also for fish muscle, spiny lobster liver, and hermit crab skeleton. Note: *Tridacha* is a clam. (Modified from Seymour, 1963b. Reprinted with permission of Van Nostrand Reinhold, Inc., New York, copyright 1963.)

- Of all the organisms collected at sea, the plankton contained the highest concentrations relative to the surrounding water. The average ratios of plankton activity to seawater activity varied, but were very significant, e.g., seven thousand times the surface water in the *Taney* survey, two thousand times the surface water in the *Marsh* survey.
- Radioactivity in other life forms reflected that in plankton, modified by the place the given form occupied in the food chain and the extent to which it fed on plankton or on organisms that consumed plankton.
- The continuous monitoring of the sea water was made possible by an ingenious device invented by Harry Levine at the New York Operations Office

and watched over by John Harley. Except for gradually becoming contaminated and thus operating at higher and higher background levels, it worked very well.

6. There were significant differences in the distribution of fallout radionuclides between marine and terrestrial environments. Fission products played an unexpectedly small part in the marine environment samples around the Pacific Proving Grounds. Much of the activity in plankton and in many fish samples was from radioactive cobalt, zinc, iron, etc., activation rather than fission products. Strontium-90 was much less prevalent than in terrestrial environments.^(a) It was suggested that the strontium (as well as the cesium) was being carried to the ocean bottom by the coral dust in the fallout.
7. Many previously unknown currents were found in the Pacific through tracing the movement of radionuclides.
8. There was no question that the biota contributed to the persistence and transfer of fallout radionuclides in the sea. Instead of filtering gradually to the bottom and staying there, the radionuclides were taken up by plankton and then passed up the food chain again. Also, the plankton themselves helped to move the radioactivity by their diurnal migrations in response to the light cycle and their movement with currents. This phenomenon was of greater importance in shallow water areas with abundant life than in the open Pacific.
9. Migratory forms of sea life could, to a small degree, bring contamination to areas that would not have received it otherwise.
10. Despite the magnitude of the effort, we must remember that these measurements were still essentially spot-checks of a vast area. Even though the later, more leisurely cruises gathered more samples and covered more points, we cannot guarantee that some "hot spots," such as those described in and around the Nevada Test Site (see later section), were not missed. Fortunately, if any did occur, they had a high probability of being in areas uninhabited by people.

4. Marine and Terrestrial Biota at the Pacific Proving Grounds

Much of the research not yet cited was more pertinent to the effects of external radiation than to the movement and effects of radionuclides in fallout. Yet, there is substantive work that has been touched upon only lightly elsewhere in this chapter. This section presents a brief review of these studies using the chronological format we have tried to follow throughout this book. The work on biota and ecological aspects continued long after the testing of weapons ceased. The NRDL went out of existence (chapter 13), but new blood was added by the entry of the Lawrence Livermore Laboratory (LLL).

a. The 1950s

The immediate surveys of the contaminated islands included, in addition to the work on aquatic forms, the collection and evaluation of domestic and wild animals and collection of many plants. In the first major published work (AEC 1956), a section is devoted to internal contamination of animals. Chickens, chicks, swine, ducks, and one cat were collected from Rongelap and Utrik and

(a) Note that this same phenomenon was noted in the long-term Columbia River surveys (chapter 11).

shipped to the United States NRDL, along with some fish and a large clam. Also, a few animals that died in the field were necropsied, and tissues were collected.

Urinary excretion showed appreciable amounts of ^{89}Sr , some ^{140}Ba , and rare earths in a quantity between the strontium and barium. From excretory measurements and tissue content measurements, body burdens were estimated and their decrease with time shown to be consistent with laboratory findings. Also, autoradiographs of the long bones from chickens and pigs showed heavy deposition of activity (mostly the alkaline earths) in the calcified areas, again consistent with laboratory findings with the fission products. Ninety percent of the activity was in the skeleton.

Fertility and hatchability studies were carried out on chickens beginning at 3.5 mo after detonation. There were essentially no significant differences from unexposed chickens.^(a) Fertility of the hens remained normal too.

It turned out that the level of internally deposited radioisotopes in the pigs of Rongelap was an order of magnitude higher than in the Marshallese people because of the more prolonged residence of the animals in the contaminated area. The chickens matched the pigs on a per unit body weight basis (AEC 1956, p. 91).

Fish caught in the waters of the lagoon were considerably more contaminated than the land animals studied in these early surveys. Also, much more of the total beta activity was in the viscera of the fish than in the animals. In 1956, at an AEC-Department of Defense (DoD) symposium, Cohn reported on the persistence of radioactive contamination of both land and marine animals two years after Operation Castle (Cohn 1956). Some native rats were added to the roster of animals already mentioned. The difference in relative importance of elements like zinc and cobalt in the marine forms compared to the terrestrial forms began to be very apparent in this work.

At the same symposium on the hazards of fallout, H. V. Weiss, also from NRDL, showed figures for many plant species, as well as animals. There were wide differences among plants, e.g., portulaca was many times more active than other plant species from the same place. However, there were enough differences between individuals to promote caution in making generalizations. About all that could be said was that predictions of possible intake by humans of fallout deposited on or in plants would require many specimens and much averaging. The islands as a whole were fairly consistent in the average amount of activities in plants. Soil activities showed the same trends, i.e., by the end of two years the amount in plants correlated well with that in soils, a situation that does not hold at early times because of foliar deposition. The primary contaminant in coconut, papaya fruits, pandanus, and arrowroot tubers was ^{137}Cs , plus significant amounts of rare earths in papaya and arrowroot tubers. Strontium-90 was in low concentration in all of these edible plant materials by the end of two years. The leafy structures had much more of the rare earths than of ^{137}Cs ,

(a) Dr. Stanton Cohn, who spearheaded much of the collecting and the work at NRDL, finally got an opportunity to try out the decorporation agents, EDTA and zirconium citrate, that he had originally been ordered to take with him to the Pacific (see p. 897). Eight chickens with relatively large body burdens did excrete more beta-active radio-nuclides during treatment, but the increase in rate was not sufficient to reduce the body burdens significantly (more in chapter 19).

illustrating again that the fallout radionuclides are far from uniformly distributed in plants. A summary of a few of these data is shown in table 12.6, taken from the paper by Weiss (1956).

TABLE 12.6. Average Relative Composition of Nuclides in Plants, Soil, and Water
— Marshall Islands —

Source		Number of Samples Averaged	Relative Composition (percent)			
			Cs ¹³⁷	Total Rare Earths	Sr ⁹⁰	Ru ¹⁰⁶
Plant:	Part	Plants				
Portulaca	Whole	1	48.9	39.2	11.8	
Papaya	Fruit	1	79.8	17.8	2.5	
	Husk	3	98.2	1.1	.7	
	Meat	2	98.9	.05	1.0	
Coconut	Shell	2	99.5	.4	.1	
	Milk	1	99.6	.2	.2	
	Leaves	2	8.3	86.5	.4	5.1
	Keys	2	92.6	2.2	5.5	
Pandanus	Leaves	2	72.7	13.3	5.1	8.9
	Air root	2	88.9	10.3	.8	
Arrowroot	Tuber	1	75.4	16.8	1.0	6.8
	Leaves	1	11.7	83.9	3.0	1.4
		Soil				
Depth, 0-1 in.		2	.34	83.8	5.6	10.0
Source:		Water				
Cistern		2		64.4	35.6	
Well		2		100	0	
Lagoon		2		94.5	5.5	
Ocean		2		100	0	

Source: Modified slightly from Weiss 1956.

More details on the internal contamination of animals can be found in the second AEC report (Dunning 1957a). Considerable emphasis is placed on the large decrease in gross activity with time of all objects, animate and inanimate. Decreases of two orders of magnitude over a six-hundred-day period were quite characteristic, as might be expected. (See, for example, Dunning 1957a, p. 6-7.)

Of special interest to possible long-term survival of animal life after extensive fallout contamination is a study by the group from the Applied Fisheries Laboratory and later the "Eniwetok Laboratory." This concerned the rats of Enjebi, a highly contaminated island. We can tell the story best by excerpts from Hines's description of the work:

The question concerned the colonies of rats on Engebi Island. Periodic sampling and observation of the Engebi colonies had been conducted, by 1955, for more than six years, a period in which Engebi had been the site of two atomic shots, within the radius of destruction of two thermonuclear detonations, and the scene of repeated and extensive engineering operations incidental to testing. The twelve months of continuous work in the Pacific after Operation Castle had provided,

however, the first opportunity for consistent and detailed observations of the rats as residents of Engebi. In view of the known experience of Engebi Island as a nuclear test platform, the question now arose insistently as to how the rats had been able to survive repeated nuclear blasts and to continue to rebuild their numbers in a radically altered and frequently highly irradiated environment.

Few spots on earth had been exposed to more prolonged periods of violence than Engebi. In the years between 1944, when the island had been subjected to preinvasion bombardment, and 1954, when it felt for the fourth time the impact of nuclear detonation, Engebi's 250-acre triangle had become a barren, sandy plot from which the coconut palms and other trees had long since disappeared and on which the most significant features were man-made structures, including the great reinforced concrete building that had survived the pressures from the Mike shot on Elugelab in 1952. From 1948 to 1952, Engebi had been a principal collecting area for rat specimens, even though the island had been the site of the early atomic detonations in 1948 and 1951. After the Mike shot, the search for rats had extended over Engebi, Biiijiri, and Rojoa Islands, but only on Biiijiri, nine miles from the point of explosion, had specimens, weak and ill, been found. Engebi was much nearer than Biiijiri to the Mike site (the center of the island was 3.2 miles from ground zero), and the low terrain had been exposed to a sequence of forces which included thermal radiation, initial nuclear radiation, shock, water waves, and residual nuclear radiation. Members of the Laboratory group, inspecting Engebi briefly a week after Test Mike, had seen the effects of these forces and had encountered beta-gamma radioactivity at a level of 11 roentgens an hour. No living animals except the transient birds could be found, and thus they had reported that there was "little probability that any rats survived on Engebi." But while it may have been unreasonable to expect that rats had survived, some had done so. Furthermore, rats survived the Nectar test of 1954, when a device detonated in the Mike crater had sent another surge of contaminated water over Engebi. By 1955, grass and scrub vegetation was sprouting on the island again, and in this new cover colonies of rats were establishing new runs and burrows. The colonies were being rebuilt even though the population had been subjected not only to physical shocks of unprecedented force but to amounts of radioactivity sufficiently high to cause the early deaths of individual survivors and genetic changes in offspring. . . .

Residual nuclear radiation levels following the Mike shot were very high. Animals aboveground would have received 2,800 to 6,700 roentgens during the first hour and those in the burrows 112 to 1,120 roentgens. During the first nine days following detonation, rats in burrows received 250 to 2,500 roentgens of total integrated dose. Cumulative levels probably were higher as a result of radioactive materials being washed into the burrows by the surge of water from the Mike crater, and the percentage of rat survival probably was extremely low. Because the Nectar device of 1954 was detonated over the Mike crater, water was lifted into the column and both thermal and residual nuclear radiations were of lesser effect. The total integrated residual nuclear radiation dose for the center of the colony a week after the Nectar detonation was 65 roentgens of gamma and 290 roentgens of beta-gamma activity. Animals in the burrows, it was calculated, would have received a maximum of 55 to 80 roentgens of beta-gamma if they stayed in the burrows for most of the week. Several animals collected nine days after Nectar had beta burns as well as thermal burns, however, and even during the later visits to the island it was not uncommon for members of the Laboratory staff to collect living rats on which losses of patches of fur and searing of the flesh testified to their exposure to sources of residual beta radioactivity. . . .

Studies of the effects of internal exposure of the rats were conducted by Lowman at the EMBL [Eniwetok Marine Biological Laboratory] and, later, at the University laboratories. Radioactive materials had entered the bodies of specimens, he found, by inhalation, by ingestion of contaminants in water and food and on the fur, and through open wounds. Iodine 131 appeared to be the principal isotope gaining

entry by inhalation. After the Nectar detonation concentrations in the thyroid were at levels considered excessive, but specific radioactivity in organs and tissues changed with time and within nine weeks activity in the thyroid was so low that measurement was difficult. The day following detonation of the Nectar shot, specific activity of the skin was just below that of the thyroid, with activity still lower in the gut, bone, lung, kidney, muscle, and liver. Within five weeks, however, specific activity was greatest in the bone of random specimens and continued to be so for the remainder of the year. Chemical separations, decay curves, and absorption curves indicated that most of the radioactivity in muscle was due to the presence of cesium 137, and no strontium 89-90 was found in that tissue. In bone, however, isotopes included rare earths (approximately 20 per cent), small amounts of zirconium and niobium, and strontium 89-90 at a level of about 10 per cent of the total activity present. In January, 1955, the bones of rats contained strontium 89-90 in amounts approximating the maximum permissible dose, but no bone tumors had been discovered and none was found in specimens collected later. In general, the deposition of radioactivity within the bodies of the rats followed familiar patterns. In a report in May, 1955, Lowman said: "In view of the fact that this population had been subjected to high levels of radiation capable of producing genetic effects in the survivors as well as early deaths of others, observable effects upon the present inhabitants should have occurred. However, the pregnancy rate and the average number of embryos per litter do not vary significantly. . . . The sex ratio does not vary from a 50-50 ratio. Except for those taken shortly after detonation, almost all individuals examined during the last year appear to be in good physical condition. . . . In addition, the main colony is expanding both in numbers and in occupied area."^(a)

The bearing of these findings on possible survival of other populations exposed to heavy fallout requires study. The behavior of fallout radionuclides in marine biota as determined during the earlier studies of the 1950s has been reviewed in previous sections.

A useful summary of the radionuclides identified in a number of life forms and in soil and ground water from the work at Rongelap Atoll in the 1950s is given in figure 12.11.

b. Postlude

The level of activity in biological and ecological research naturally decreased markedly after the cessation of tests at the Pacific Proving Grounds. Nevertheless, the biologists were firm in their resolve to get as much of the long-term picture as possible. Thus, the medical return visits were almost always accompanied by some people who took samples of water, food, and general biota. Some of the work came from expeditions concerned more with worldwide fallout than specifics of the Pacific Proving Ground. Yet, the efforts were mutually helpful.

A considerable stimulus to further research at the Proving Ground was the continuing concern over repatriation of the Marshallese described earlier. In 1963, a Biomedical Research Program was established at LLL (chapter 13). Its primary charge was to study the effects of early fallout. On request from Washington, the LLL people went deeply into analyzing the health risks of resettling the atolls. They mounted a comprehensive analysis of the radionuclides present, their transfer within the environment, and from the environment to food. They looked especially at what exposures might result from eating crops raised on the islands, drinking the water, or eating fish caught from the lagoon.

^(a) Hines 1962 (pp. 206-207; 210-213), who quotes from Lowman 1955.

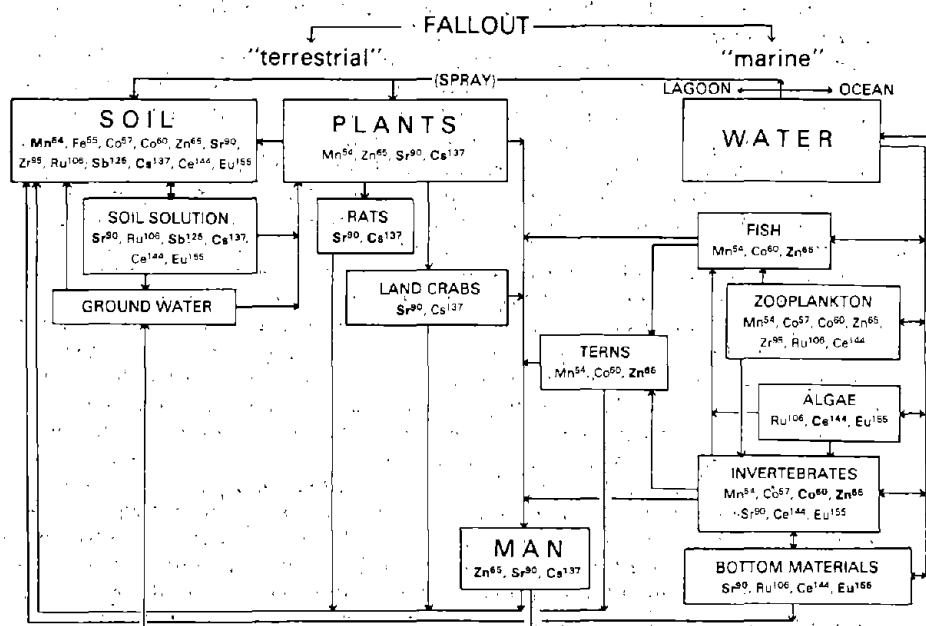


FIGURE 12.11. Distribution of fallout radioisotopes at Rongelap Atoll, 1959. The more important (i.e., dominant) radionuclides are indicated in bold type within the groups. Note that the terminology of the day is used. (Reset from Hines 1962 using data by Held; Reprinted with permission of University of Washington, Seattle, Washington, copyright 1962.)

As frequently occurs when a new organization enters a field, the people from LLL acted as though nothing was known before.^(a) While this was not true, as we have already seen (check for example figure 12.11), there is no question that much more was known when their studies came to maturity. The level of sophistication was also increased to include large data banks and computer models for dosage estimation. A new feature was consideration of the role of residual plutonium and other transuranics. We will review some of the pertinent work in the decades since 1960 as cryptic listings:

1. At the first Radioecology Symposium (chapter 11) Lowman (1963) of the Puerto Rico Nuclear Center, reported on the radioactivity of tuna and plankton from the Central Pacific. The contamination came largely from the Hardtack I series in 1958. The tuna specimens, over one thousand of them, were obtained from fishing vessels landing at Japanese ports.^(b) It appeared that three factors controlled the uptake of radionuclides from sea water:

(a) "When we began there were no data on inventories of radionuclides in soils and water. Nothing was known about their movement from one part of the environment to another. . . ." From brochure on the LLL Biomedical and Environmental Research Program (undated).

(b) Dr. Toshihara Kawabata (National Institute of Health, Tokyo) was instrumental in providing the fisheries' samples to Dr. Lowman.

isotope dilution by the corresponding stable element; complex formation between divalent cations and biological materials; and the metabolic requirements, or lack of them, for certain elements. Uptake patterns at three trophic levels, plankton, omnivorous fish, and the carnivorous tunas, showed clear evidence of discrimination for or against certain radionuclides.

2. A careful study by Held (1963), University of Washington, of the qualitative distribution of radionuclides at Rongelap over five years after fallout contamination indicated that ^{90}Sr , ^{125}Sb , and ^{137}Cs were the principal nuclides entering the soil. However, in land plants and plant-eating animals, ^{137}Cs was the highest, with ^{90}Sr in lesser concentration. The marine organisms continued to show the entirely different cadre of radionuclides as described in the previous section of this chapter. Also, it was different in different groups, i.e., plankton versus algae versus marine invertebrates versus fish and sea birds. It became quite clear that the body burden of any humans of the area would be very dependent on the diet qualitatively as well as quantitatively.
3. A description by Welander (1969), University of Washington, expanded on the distribution of radionuclides in the environment of Enewetak and Bikini Atolls. This was expanded upon further by Jackson and Carpenter (1969), with a description of radioisotope cycling in terrestrial communities at Enewetak Atoll.
4. Later work by Held (1971) and others used tuna from the Japanese fisheries and from the vicinity of Bikini and emphasized the increasing role of ^{55}Fe in light and dark muscle and in liver. It was suggested that some of the ^{55}Fe came from USSR tests of 1962 and was deposited in narrow bands related to the test sites at 75° and 52° N, since specimens from the southern hemisphere were much lower. Held references several other studies involving ^{55}Fe . Interestingly, the concentrations of ^{137}Cs were found to be about the same as those reported in the 1960s (Seymour 1963a; Folsom and Young 1965). Yellow fin tuna from Bikini Atoll contained ^{60}Co believed to have been derived from the atoll. As before, the catches re-emphasized the large variability that can be encountered in specimens with no obvious reasons for a difference.
5. More work on ^{55}Fe was published by Schell in 1975, which emphasized especially the partition among water, suspended particles, and colloids. Schell believes that the primary source of this ^{55}Fe was the barges used to hold the fission devices in the lagoon and the iron buildings that housed the thermonuclear devices on the atolls. He cites the large concentration factors for iron by phytoplankton (25,000) and zooplankton (15,000) and the significant transfer of ^{55}Fe through the food chain. No work was done to show possible biological effects, but it is significant that despite the "70-fold decrease in radioactivity by decay since the last nuclear detonation at Bikini in 1958, some sediments contain concentrations of ^{55}Fe as great as 300 pCi/g dry weight" (Schell 1975).
6. Data on ^{137}Cs and ^{60}Co in soils, plants, and rat tissue samples were collected on Runit, one of the more contaminated islands. These were presented by Bastian and Jackson (1975) from Bowling Green State University in Ohio. The amounts in animal tissue ranged between 0.5 and 500 pCi/g, in plants between 2 and 200 pCi/g, and in soil (the first 50 cm) between 0.1 and 2 pCi/g. Obviously, the living tissues were able to concentrate the nuclides from the soils. The data agreed well with AEC information, but note the very large ranges.

7. There was a long series of studies from the LLL Some of these are:(a)
- a. *Dose Estimates for the Marine Food Chain* by Robison (1973)
 - b. *Terrestrial Biota Survey at Eniwetok*, by Koranda et al. (1973)
 - c. *Radioactivity Levels in Enewetak Soil*, by Gudiksen and Lynch (1975)
 - d. *Transuranics and Other Radionuclides in Bikini Lagoon: Concentration Data Retrieved from Aged Coral Sections*, by Noshkin et al. (1975)
 - e. *Evaluation of Plutonium at Eniwetok Atoll*, by Wilson, Ng, and Robison (1975)
 - f. *Plutonium Levels in Kwajalein Lagoon*, by Noshkin, Eagle, and Wong (1976)
 - g. *Evaluation of Water Quality*, by Noshkin et al. (1977)
 - h. *Plutonium Concentrations in Fish and Seawater from Kwajalein Atoll*, by Noshkin, Wong, and Eagle (1979)
 - i. *Transuranium Radionuclides in Components of the Benthic Environment of Eniwetok Atoll*, by Noshkin (1978, 1980)
 - j. *Reassessment of the Potential Radiobiological Doses for Residents Resettling Eniwetok Atoll*, by Robison et al. (1980)
 - k. *Radionuclide Concentrations and Dose Assessment of Cistern Water and Groundwater at the Marshall Islands*, by Noshkin et al. (1981)

There is no doubt that even now (1985) the lingering contamination on these atolls and islands with cesium and to a lesser extent, strontium, is a major obstacle to the much desired resettlement of the several Marshallese populations. We will see details in other connections. Suffice it to say here that the measurements must be continued. Also, let it be emphasized that some extremely embarrassing mistakes, in terms of both health effects and political interrelationships could have occurred if the researches described in the previous pages had not been taken seriously and continued at a significant level. There is no indication that we are yet "out-of-the-woods." What may seem to many to be a never-ending enterprise has proven its worth and the need for its continuation. Also, the research results have contributed and continue to contribute significantly to our knowledge of the movement of radionuclides in the environment, particularly the role of "recycling," as we will see in chapter 15.

The work on the transuranics requires comment. It appears that the lagoon water, most of the time, contains concentrations of $^{239+240}\text{Pu}$ (and ^{241}Am) similar to concentrations from global fallout. Yet, samples of fish in 1972 contained considerably higher concentrations. This work predicted elevated concentrations in humans, if the reef species of fish were eaten regularly, of 25% of the radiation protection guide (RPG). Later work indicated that the 1972 collections of fish had unexplained high concentrations of transuranics and that there was probably some mistake. The 1979 work (Noshkin, Wong, and Eagle 1979) showed much lower concentrations in fish and resulted in a calculated dose rate from the marine pathway of only 0.005% of the RPG.

On the terrestrial side, there were local areas of high plutonium concentration. But the average was well within even the new Environmental Protection Agency (EPA) limits. Nevertheless, it was clear that the local "hot spots" would have to be cleared up before anyone could move back for regular living on

(a) These are only samples. There are many more on the same general subjects in UCRL reports.

some of the islands. As a recap of the many findings regarding the biota at the Pacific Proving Grounds and the problems solved regarding fallout contamination, we turn to a summary prepared by Hines (1962). While this does not address the most recent work and says nothing about the transuranics or problems of repatriation, it stands as a good review of the landmark research findings. It considers the thrust of the biological and environmental work in the Pacific from Crossroads to the cessation of testing.

It was known, for example, as it had not been known in 1943 and as it had been realized only faintly in 1946:

- that in the natural environment the extremely efficient biological uptake of nutritive elements can be measured in the uptake of the radioactive counterparts of such elements;
- that the levels of uptake of radioactive elements by the biological organism will be affected by the character of the organism — its physical complexity, its mineral needs, its metabolic processes — and by the chemical and physical form of the radioactive isotopes, the availability of stable isotopes, and the conditions of the environment;
- that radioactive elements, because they are identifiable, can be followed through food chains and biological systems virtually to the limits of their detectable lives, and that studies of elements in nature thus can be pressed much further than previously had been considered possible;
- that in aquatic environments the basic organisms, such as those comprising the masses and plankton and algae, not only are more resistant to the effects of radioactivity but are capable of blotting up quantities of radionuclides and thus placing them at the threshold of the biological system;
- that in the natural environment the circulation of radioactive elements involves both water and land, and that between the two there will be environmental transfer, some “uphill” from water to land and some “downhill” as elements are rinsed or leached from soils or plants and carried to the rivers or oceans;
- that products of nuclear fission, significant on land, are far less so in sea water, and that, on the other hand, the nonfission products such as radioactive forms of iron, cobalt, manganese, or zinc may contribute up to 100 per cent of the radioactivity found in aquatic organisms, from the plankton and algae to the larger fishes;
- that radioisotopes introduced in large quantities into the ocean (either by initial mixture in an underwater release or by fallout after an atomic explosion) are transported both by ocean currents and by ocean organisms, but that the physical movement will be affected by the biological conditions and modified by biological rules and processes;
- that masses of radioactively tagged water may be followed and measured across thousands of miles of ocean, much farther and longer than had been supposed possible before 1954 and 1955;
- that strontium 90 and cesium 137, among the long-lived radioisotopes of greatest public concern, are found only in low amounts in marine organisms studied under field conditions, and that the radioisotopes found in fish, for example, are predominantly the shorter-lived nonfission products elements such as iron, zinc, or manganese;
- that certain biological species, because their physiological needs are known and their places in the food chains established, may be used as reliable indicators of the nature and probable extent of the radioactive contamination of a natural environment at any point in time;
- that populations of animals and plants observed under field conditions—the sea urchins of Bikini in 1947, the grasses and shrubs restoring the natural cover of Eniwetok’s shot islands, or the rats of Engebi — exhibit a capacity to maintain themselves even in environments that have been exposed to the full effects of nuclear blast and to levels of radioactivity that all laboratory experience indicated were totally lethal;

—and that every release of radioactive products in nature whether by atomic detonation, by accident, or in the disposal of industrial wastes, sets up a biological reaction peculiar to the place and condition of the release itself; that the variables are almost infinite in number; and that the individual situation can only be assessed by conducting observations with a knowledge of the biological rules governing the disposition of radioisotopes in the natural environment.
(Hines 1962, pp. 306-307)

The above can be considered as among the “knowns” worked out in research at the atolls. Among the many unknowns is the *ultimate effect* on biota of fallout of the magnitude experienced in the Marshall Islands. While the resiliency of nature was demonstrated on many occasions, vast areas of oceanic radiobiology remain essentially unknown. These can be studied profitably only by an organized and well-financed attack.

IV. Trinity Revisited

In the summer of 1945, after the shot at Alamogordo (section II A), the Los Alamos people revisited several suspect houses and barnyards and gathered evidence that the Chupadera Mesa area had remained “hot.” However, the pressure of other things (e.g., Crossroads) prevented further follow-up until August 1947. At this time, a combined survey team of biologists and chemists from UCLA and the University of California, Berkeley, under the supervision of Wright Langham from Los Alamos, spent three weeks working over the area. They were able to cover about one hundred square miles. The results were issued in a classified report in several sections covering soils (Overstreet et al. 1947; Overstreet, Jacobson, and Larson 1947), botany (Dunn and Levine 1947), ornithology (Van Rossem 1947), mammals (Brauner 1947), herpetofauna (Lowe 1947), and entomology (Mattoni 1947).^(a) The results of this survey indicated several interesting facts:

1. Residual radioactivity was definitely present in the grasses and was found in cattle feces.
2. The activities were definitely higher in some of the more distant areas than close to ground zero.
3. There had not been much leaching down of the soil activity. It had remained in the first centimeter or so near the surface. Since most of the desert plants have fairly deep roots, the fission products had not been taken up to any appreciable extent from the soil. The exception was the shallow-rooted grasses, but much of their activity might have been surface deposition.
4. No signs of radiation injury were seen in the animals collected.
5. Some plants were growing back in the center of the crater, evidently from underground roots and windblown seeds. There were practically none toward the periphery of the crater, which gives the idea that the temperatures may have been higher there than in the center.
6. One region of high activity, the Chupadera Mesa (see section I A), was being used extensively for cattle grazing. Calculation indicated that a

(a) I am indebted to Jack Healy, Los Alamos, for making available copies of these reports, which he had obtained in turn from Pat Durbin at Berkeley. They were in Joe Hamilton's files since he sponsored the Berkeley contingent of the survey team.

- 1,000-lb cow might ingest as much as 600 μ Ci per month or 7.2 mCi per year of fission products, and this was based on present, not earlier, activities. This caused considerable concern.
7. There was no evidence of genetic change in animals, plants, or insects; not surprising in view of the times needed for mutations to be expressed.
 8. The area covered by the fallout was obviously much greater than suspected from the survey in July 1945.
 9. It was conjectured that the "hot" area on Chupadera Mesa was the result of several phenomena: (a) the initial cloud hovered over the ground zero and adjacent areas during the morning hours because there was very little air motion; (b) as the day progressed, the usual thermal breeze started and the cloud began to move; and (c) the characteristic midafternoon summer thunderstorm washed out the cloud over the mesa and deposited an appreciable portion of its activity.
 10. There were many puzzles with regard to distribution of the fallout, the transfer into and about the biome, and the characteristics of the repopulation forms and processes.

It is unfortunate that these reports, while declassified in March 1972, have never been published. They are full of detail and replete with maps and illustrations.

In 1947, Stafford L. Warren, the medical director for the MED up to its disbanding, instigator of the Columbia River surveys (chapter 11), and caretaker of the safety of Operation Crossroads (section II-C of this chapter), settled at UCLA as director of the newly organized Atomic Energy Project of UCLA and as dean of the new medical school about to be built. He maintained his keen interests in the problems of fallout and the biomedical aspects of weapons testing by proposing to AEC further visits to the Trinity site. In a long letter to Brigadier General James McCormack, Jr., AUS, Military Application Division, USAEC, he pointed out the growing tendency for use of that land for cattle grazing, the digging of wells, and other reasons to know what was there. He suggested several summer surveys using graduate students and other individuals with lowered commitments in summer and a permanent organization to guide and interpret the effort. The enterprise was approved and, naturally, the permanent organization chosen was the UCLA Atomic Energy Project! Thus began a decades-long association of the project with the weapons-testing program, especially in the area of terrestrial phenomena. The collaboration with Los Alamos continued, particularly for doing the radiochemistry and for continuing opportunities to tap the deep Los Alamos experience in people like Wright Langham and Thomas Shipman.

Since Warren was busy building a medical school, the work had to be carried forward by staff of the project. Chief among these was Kermit H. Larson, the rest of whose career was devoted to understanding what went on at the test sites. J. H. Olafsen, J. L. Leitch, A. W. Bellamy, E. M. Romney, and many others were also included.

The efforts toward further survey of the Trinity site were contained in UCLA project reports (Overstreet et al. 1947; Bellamy et al. 1949; Leitch 1951; Larson et al. 1951a, b; and Olafsen et al. 1957). As the report titles indicate, the emphasis changed gradually from the fission products to plutonium and the actinides, as occurred also at the Pacific Proving Grounds.

These researches became the basis for the UCLA Laboratory's assessment of contaminated landscapes in general. They showed clearly the irregular patterns

of fallout deposition and the presence of what appeared to be "hot spots" like the Chupadera Mesa.^(a) The amounts of activity in mammals did not correlate with dose-rate patterns put down for the fallout contours. Soil properties and the chemical nature of the fallout materials played an important role.

Toward the end of the revisits to Trinity, it became very hard to measure any activities above background for the fission products, so attention turned to the long-lived actinides.^(b)

In general, the findings confirmed the earlier work. There was no doubt that the radioactivity outside of the crater increased with distance out to as much as eighty-five miles. The maximum occurred at about twenty-eight miles from ground zero, and the activity then decreased but was easily measurable out to eighty-five miles.^(c) This was true of soil (surface layer only) and of both animals and plants. Even after many years and scores of rainstorms, activity deposited on the leaves of some plants was almost impossible to remove.

Interestingly, the concentrations in animal tissues that were very low in the first two years began to be detectable in 1949 and 1950 in, for example, the pack rat. There was activity in liver and bone as well as in the digestive tract. Activity in plants rose similarly but somewhat earlier. These data point to some sort of accumulation process. Was the material being solubilized and thus becoming more available? Laboratory work has been directed toward this point, as we will see in chapter 13. It shows that solubilization processes can take place and that the chemical form of the isotope may not be constant over time. It is also interesting that considerable variation in chemical form can occur, even in a relatively circumscribed area like the Trinity site.

Relatively little of the early UCLA work on Trinity has been published in the open literature except for plutonium work.

Even though the people at Los Alamos had pioneered the environmental work at Trinity, they were too occupied with the Pacific and problems of worldwide fallout (sections III and IV) to do much more than help with the August 1947 resurvey. However, they did re-enter the field for determination of environmental plutonium at the Trinity site at twenty-seven and twenty-eight years after the event (Hakonson and Johnson 1974; Nyhan, Miera, and Neher 1976). Both of these efforts concentrated on soil contents and the behavior of plutonium in soil, but they included also samples of grasses, shrubs, and trees, and of rodents. Some of their data are shown in table 12.7.

These data indicate that amounts of plutonium do indeed seem to be higher at certain points along the fallout pathway. Note, for example, the relatively high values in the top section of soil as far out as 40 and 56 km and the apparent concentration in lungs of rodents at 32 and 40 km compared to even 0.1 and 48 km. (Is there a special area for dust inhalation?) Also note that grasses are consistently higher than forbs, shrubs, or trees. Indeed, all of the vegetation but the grasses was essentially at background levels.

(a) Later work has called into question some of the hot spots indicated in earlier work at the Nevada Test Site (NTS), but the presence of "Hot Canyon" and Chupadera Mesa as hot spots has held, as have the probable reasons for their existence.

(b) Larson (1979) emphasizes that only a small fraction of the plutonium in a fission device is consumed in the detonation. Most of it is carried aloft and can be distributed over wide areas.

(c) This raised questions as to whether or not the surveys should be expanded to a considerably larger area.

TABLE 12.7. The $^{238-239}\text{Pu}$ Content of Some Ecosystem Components Collected in the Fallout Zone of the Trinity Detonation(a)

	Kilometers From Ground Zero (GZ) Along Fallout Pathway								
	GZ	0.1	8.1	16.1	24.1	32.2	40.3	48.3	56.4
Soils (fCi/g dry)									
0-2.5 cm	254812	36	434	311	125	295	668	278	1442
2.5-7.5 cm	262720	36	0	331	746	116	344	20	89
7.5-30 cm	61858	23	6.6	213	175	3.4	62	10	35
Vegetation (fCi/g wet)*									
Grasses	768	169	73	34	5.1	15	19	11	28
Forbs				3.0	0.60	2.5	4.7	5.4	26
Shrubs/trees	6.2	2.4	9.5		1.9	4.1	6.5	0.60	2.2
Rodents (fCi/g wet)*									
Liver		12(11)**	4.4(2.2)	1.3(0.8)	1.7	2.3(1.5)	4.5(2.7)	6.2	
Lungs		25 (19)	11 (8.1)	4.1(3.0)	3.3	48 (27)	50 (45)	0	
Hide		4.8(0.96)	5.6(2.3)	2.0(2.0)	0.75	3.4(1.2)	2.8(1.1)	3.8	
Carcass***		3.2(1.2)	15 (8.0)	4.2(3.0)	0.84	30 (29)	4.7(1.6)	2.5	
No. of samples		4	5	3	1	5	4	1	

*Species comprising the vegetation and rodent samples are given in the text.

**Parenthetic value represents the standard error of the determination.

$$\text{Standard Error} = \frac{\text{standard deviation}}{\sqrt{\text{No. of samples}}}$$

***Carcass includes skeleton and skeletal muscle.

(a) Twenty-seven to twenty-eight years later.

Source: Reset from Hakonson and Johnson 1975.

Comparison with earlier samples indicated that the plutonium had finally, after twenty-seven years, gone down into the soil to at least 30 cm, whereas in the earlier resurveys it seemed to be fixed in the uppermost layer. This process was not so marked at distances beyond about 24 km. The gross distribution after twenty-seven years indicated some increased migration of plutonium but basic agreement with the UCLA findings many years before.

The twenty-eight-year survey did size-activity analyses. There was more plutonium associated with small particle sizes (less than 100 μm) at greater distances from ground zero and as soil depth increased. Neither is surprising, of course, but such factors have an important bearing on possible availability to biota.

Finally, the Los Alamos workers, Hakonson and Nyhan (1980), produced a comprehensive summary of plutonium distribution at Los Alamos compared to Trinity. This was in Hanson's book, *Transuranic Elements in the Environment*, described in chapter 11. Concentration in herbaceous vegetation was related to that in soils from all sites and is believed to indicate external contamination rather than uptake through the root system. Certain rodent tissues also correlated well with soil plutonium, and most of the plutonium was associated with pelt and gastrointestinal tract in the native rodents. This again indicates a dominance of "physical processes" (e.g., ingestion of dirt, dust on the pelt,

inhalation of dust) over metabolic processes. There was no evidence for increase in plutonium concentration as it passes through different trophic levels, i.e., soil to vegetation to animal. About the only difference between Los Alamos and Trinity was the dominance of water as a transport vector at Los Alamos and of wind at Trinity.

The experiences gained in the resurvey of the Trinity site provided excellent background for what was to come at NTS. In fact, the work could be more unified and uncomplicated because there were no other tests occurring to deny access to important areas, or to introduce the complexities of new fallout to confuse identification and measurement of the samples. Obviously, the Trinity resurvey was largely a Los Alamos and UCLA show.

V. The Nevada Test Site

A. The Arrangements and Events

The decision to open a site for testing of nuclear weapons in the continental United States was partly a result of the Korean War. The logistics of supporting the Pacific Proving Ground were strained by the need for naval vessels and planes in the Far East. Also, the Cold War was developing. The pressures to perfect devices without the long trek to the Pacific spurred Los Alamos to urge a quick program to check design revisions at a site nearer to the laboratory. Also, the need for a more or less permanent test site for the "small" weapons further spurred agitation for a continental test site.

The Air Force had for many years maintained a very large bombing and gunnery practice range over an area in Nevada beginning about fifty miles north of Las Vegas. After many studies during summer and fall of 1950 (Hacker, undated), President Truman approved the choice of a portion of that area as a nuclear-weapons test site. A base camp was set up at a spot designated as Mercury, and the tests were spread out over a vast area, largely north and northeast of Mercury. Mercury, which developed from a tent city to a reasonably comfortable complex of workshops and barracks,^(a) is about seventy miles from Las Vegas, the test sites from twenty-five to over fifty-five miles further along. Gradually, facilities for biomedical work were developed at Mercury. These started as holding quarters for mice and rats, but eventually expanded to accommodate pigs and burros among other large animals. The Army and Air Force Veterinary Corps played active roles in operating these facilities.

At the time of this writing, 569 announced shots had taken place at NTS under U.S. auspices plus 13 under joint U.S.-U.K. auspices, for a total of 582 (NVO 1982). Comparison to the total of 106 shots in the Pacific makes it appear that NTS overwhelmed all others. This was true only in terms of numbers of tests.

The atmospheric tests occurred in eight series: Ranger, winter 1951; Buster-Jangle, fall 1951; Tumbler-Snapper, spring 1952; Upshot-Knothole, spring 1953; Teapot, spring 1955; Redwing, spring and summer 1956; Plumbbob, spring,

(a) To compensate for the alternate tedium and pressure of life away from families, assigned military and hoards of engineers could get food at Mercury that was excellent and cheap. One of the ubiquitous silver dollars in a turnstile opened up an all-you-could eat, cooked to order, mountain of food. After a full day in the field, some prodigious appetites were generated and indulged.

summer, and fall 1957; and Hardtack, Phase II, fall 1958. A few of these were underground. In 1961 and beyond, all tests were underground. A large majority were weapons-related or concerned weapons effects (e.g., the Civil Effects Test Group work, which involved effects on animals and on structures). A few involved the placement of troops, the reverberations of which are now very strident. Twenty-seven were Plowshare shots and thirty-three were designated as "safety experiments." Since the purpose of the tests, except the Plowshare and safety shots, do not make much difference to the thrust of our discussion, we will not tie the discussion to specific events except for identification purposes. The Plowshare and safety shots are "special events" and will be considered in chapter 14.

While there is no question that large quantities of fission products reached the atmosphere from Nevada, many shots were relatively small. Some of them were on the order of 1 ton of TNT equivalent, although a goodly number were in the kiloton range, even as high as 43 kt,^(a) twice the yield of the "nominal" Hiroshima and Nagasaki weapons. Of the total NTS shots, only about one hundred were in the atmosphere. Nevertheless, the total contribution of these to atmospheric contamination was considerable; much of it was to the troposphere, whereas the Pacific tests nearly always had stratospheric as well as tropospheric components. Thus, the NTS work contaminated our own real estate more than others, while the Pacific activities contributed much global as well as highly active local contamination.

It has been estimated (Perkins and Thomas 1980) that about 230 megatons of fission yield were introduced into the atmosphere from all above-ground tests. The contribution of the NTS is given by Larson (1963) as about 101.3 kt up to 1961 when he wrote the paper.

Although the external dose was the primary measurement, the potential for radionuclide contamination was not lost on the UCLA and associated investigators. They, particularly Kermit Larson and E. M. (Van) Romney with or without assistants, tramped around the desert as much as possible between shots and during lulls between series to collect samples of soil, vegetation, and indigenous animals. They were sometimes joined by ecological types from other installations. We will be reviewing this work in due course.

The early RadSafe activities at NTS^(b) were provided by the Health Division (H-Division) of Los Alamos Scientific Laboratory. When Dr. Shipman, the medical director at Los Alamos, began to complain about the emptying out of his H-Division whenever tests were in progress at either NTS or in the Pacific, other AEC laboratories were tapped to supply scientists who could help out.^(c) After a quick training period, these "volunteers" were largely put into the job of mapping fallout patterns. In the interim, the responsibility for these operations had shifted from Los Alamos to UCLA, and Kermit Larson became something of a steward for the RadSafe activities, as well as others we have already discussed.

(a) Even larger ones were employed for some of the later underground shots.

(b) An extensive review of the RadSafe activities at NTS, series-by-series, will be available from Hacker. See also Dunning (1957b).

(c) All laboratories had their innings as they did for Operation Crossroads. While there was some attempt to tap special abilities, much of the work was assigned in more or less military fashion. Thus, Lauren Donaldson (see chapter 11) drove trucks, and most specialists acted as monitors. Some formed deep attachments to the desert. Others could barely wait to get home.

The military, of course, supplied much manpower, and collaboration between the military and AEC and was, of course, essential.

A short summary of the safety measures taken at NTS is given in the following from a paper prepared for the 1963 Congressional hearings and submitted by A. R. Luedecke, General Manager of AEC:

Safety at the Nevada Test Site

(By Division of Operational Safety, U.S. Atomic Energy Commission, June 13, 1963)

The health and safety of persons was, and has been, the prime considerations in selecting originally the Nevada test site and in the conduct of the nuclear tests. An exhaustive search was made before the Nevada site was selected as the most suitable one. It originally contained 600 square miles (expanded to about 1,120 square miles) adjacent to the U.S. Air Force Gunnery Range of 4,000 square miles. For purposes of general safety, as well as security, the test site is closed to the public. Aerial and surface surveys are made to insure that no one has wandered into the area.

Beyond these controlled areas are wide expanses of sparsely populated land, providing optimum conditions for maintenance of safety. Although the area is only sparsely populated the individual resident has been given full consideration. Radiation monitors have been present during times of testing and there have been occasions when residents have been relocated for a day or so to insure their safety. They have received financial remuneration for such movements. There have also been occasions when persons have been asked to remain indoors for a few hours to reduce the radiation dose though the out-of-door exposure was far from hazardous.

Before each and every nuclear detonation at the Nevada test site, a panel of experts weighs carefully all of the factors that will insure safety. On the panel are representatives from the fields of public health, medicine, meteorology, fallout phenomenology, blast effects, etc. As a result of these deliberations, more than 200 delays in firing have been made at a cost of millions of dollars, to insure safety.

The principal cause for the delays has been weather conditions, i.e., to insure minimum fallout in populated areas. A complete station of the U.S. Weather Bureau is in operation at the site with one to eight weather monitoring stations ringing the test area depending upon the type of test to be conducted. The U.S. Weather Bureau predicts downwind trajectories, precipitation, and other factors which could affect levels of fallout. The data from the weather stations are currently available almost up to the exact time of the shot. A detonation can be canceled at any time up to a few seconds before shot time. All of the meteorological data bearing upon each test are documented not only for the Nevada test site but for the entire Western United States.

(From U.S. Congress, 1963, Part I, p. 294)

This statement was referred to later in the hearings by Glenn T. Seaborg, then AEC Chairman, as typical evidence of the care taken by AEC to protect the nation's health during the tests.

It will be noted that a panel of experts (The Test Managers' Advisory Panel) was convened before each test to advise the Test Director on matters of safety. This was a senior and powerful group. Not mentioned in the quotation is the fact that the U.S. PHS usually had a representative present, and he had a powerful voice in the decision to shoot or not to shoot (Andrews 1980). This was important because the PHS was there exclusively to protect health and had none of the dilemmas some of the others had of needing the weapons data, of making people repeat the countdown operations, or of holding a group of reluctant scientists and military in a desolate and primitive environment.

Offsite surveillance was rather rudimentary in the early days. Indeed, as we will see in the next section, the extent of offsite contamination was not fully appreciated. As the need for good offsite surveillance became apparent and grew, the PHS was drawn in under contract to AEC and provided what became an extensive network. This was continued under the auspices of the EPA, which took over the network and laboratories built up by the PHS. A further short excerpt from the 1963 Congressional hearings addresses this aspect:

Full monitoring coverage has been provided offsite by the U.S. Public Health Service under contract with the U.S. Atomic Energy Commission. There have been and are extensive monitoring programs, including mobile monitoring teams, film badges, air samplers, automatic gamma recorders, collections of milk, vegetation, soil, etc. A more complete description of these programs may be gleaned by review of the attached document, "Environmental Contamination From Nuclear Explosives Offsite Nevada Test Site, September 15, 1961-September 15, 1962." The cost of these monitoring programs is about three-quarters of a million dollars per year. In addition, there are various research projects that contribute valuable information.

All of the essential data from these monitoring programs have been reported in the open literature. The principal sources for publication have been the Commission's semiannual (now annual) reports to Congress and the U.S. Public Health Service's monthly publication, *Radiological Health Data*. Spot announcements have been made of immediately available data. Also, members of the Commission's staff have published many technical articles presenting data and their analyses.

(U.S. Congress, 1963, Part I)

Melvin Carter, a PHS officer whom we have met in other connections in this book, was intimately associated with the offsite surveillance program and has supplied this author with much information. The PHS Operations at NTS were headed by Oliver Placak, another well-known and respected PHS officer. In recent years, Carter has reviewed the subject. Of particular interest is a paper he prepared for a symposium "Fifty Years of Radiation Protection" held at French Lick, Indiana, and published in a historical anthology edited by Kathren and Ziemer (Carter 1980). In addition to relating some details of the various programs, Carter emphasized the fact that many of the offsite monitors lived in the more vulnerable communities of Nevada and Utah, partook of the same life as the permanent residents, ate the same food, their children played in the same dust and, incidentally, were exposed to the same fallout.

Emphasis was placed, in both onsite and offsite surveillance, on measuring the gamma dose, and to a lesser extent the external beta dose or the combined dose. It was only by the analysis of air, milk, vegetation, animals, water, etc., that information became available for making some guesses about internal doses independent of calculations from the soil or air content. As the program developed, and especially as public concerns grew, the monitoring function was expanded by a Medical Liaison Officer Network comprising physicians in many states as well as PHS (and later EPA) personnel. Even some epidemiology was begun.

Aircraft were also used for monitoring. The military flew aircraft into the cloud from a detonation to gather samples for diagnostics on the weapons. The same or similar aircraft were used to sample distributed atmospheric radioactivity and to detect, by low-altitude passes over the terrain, deposited fallout.

A brief survey of the PHS environmental radiation surveillance activities is contained in a pamphlet prepared by the PHS (PHS 1964) and NTS; country-wide data are shown in the monthly issues of *Radiological Health Data*,

published by the Bureau of Radiological Health of the PHS. Wrenn (1981a) presented a review of external radiation dose estimates offsite in Nevada and Utah at the annual meeting of the National Council on Radiation Protection and Measurements (NCRP) in April 1980. This is best discussed in the context of internal dose estimates in later sections.

The surveillance, both ground and air, permitted a fallout contour map to be drawn for almost every shot at NTS. Through the kindness of Dr. Gordon Facer, Division of Military Applications, DOE, this author has been provided with a complete set of these maps. There is no question that gaps exist in the contours, particularly for the more rugged terrain, and there is not much information beyond relatively early times postshot. Yet, in view of the cumbersomeness of the early equipment, its limitations in sensitivity, and the fact that shots sometimes occurred daily, the amount of information set down is impressive. These maps have been of great use in some of the reconstruction activities now under way.

Unfortunately, the primary data given in the early days were the external gamma and/or beta-gamma dose rate. How well these do or do not correlate with eventual internal doses is still controversial and at the heart of many current concerns.

B. Early Experiences with Fallout at NTS

The NTS was pressed into service very quickly after the decision was made to have a continental proving ground. The decision to use it was approved by President Truman in December 1950. The first series, Operation Ranger, began on January 27, 1951, and there were four shots between then and February 6, 1951! Worry about fallout at distant cities had little chance under such pressures. There was no advance public announcement. Even people inside of AEC did not know testing was scheduled for Nevada. The lessons that might have been drawn from Julian Webb's deductions and the experience at Trinity were not heeded because those who could have brought them to bear were not involved or even informed. We can see the sequence by a short quote from the 1976 speech by Merrill Eisenbud, New York Operations Office, already cited:

Our first notice of it, apart from the fact that people were reporting booms down in Las Vegas, was when we got a call from Harry Blair, Project Director at the University of Rochester, who had just had a call from Eastman Kodak which said that the snow (it was snowing that day) was radioactive. The University of Rochester had checked the snow and found it to be radioactive, and Harry wanted to know what to do.

I needed a few microseconds to think it over then I called somebody whose name I won't mention and said, "It's snowing up in Rochester and all through the northeast, and I hear the snow is radioactive. What do you know about it?" We knew nothing about bomb phenomenology or where the stuff went or what it contained; fission products were still pretty classified stuff, and none of us even had a working knowledge of what the fission products mixture was like.

My contact at Nevada Test Site said, "You're crazy, Merrill. I was out to Ground Zero, and there's no radiation out there, and you're trying to tell me it's up in Rochester."

And that made me mad, because we had a very serious problem on our hands in that Kodak had already once been affected by radioactive fallout and now they were probably being affected again. So, John Harley and I put our heads together and took advantage of the fact that it was snowing and we called Rochester back

and called people we knew in Cleveland, St. Louis, Buffalo, Boston, and sent teams out from New York as well, and we gathered snow in quart jars. That was a Friday afternoon. By Sunday the people came back with the snow samples; and we lined everybody up with hot plates, boiled the stuff down, and put it into a form in which it could be counted; and by Monday morning we had a map of fallout in the northeast United States, which has never been published. I don't know where the map is; I asked John Harley if he knew, and he thought it was in Washington someplace. But that was the extent of the preparations for those early tests.

Our group was then invited into the preparations for subsequent tests. And we were concerned and assigned the actual responsibility for monitoring beyond the Test Site. The question was: "How far to monitor?", and, "How to monitor?" (Eisenbud 1976, pp. 4-5)

"History" can vary according to the time and place of the beholder. Dr. Howard Andrews, the PHS officer we have already met via an interview and will again in chapter 18, was associated with the Test Managers' Advisory Panel. He was in Nevada at the time of the test in question and recalls that the telephone calls were in the sequence: H. A. Blair, Test Manager and Test Director, Weather Division, Advisory Panel (Andrews 1985). While the results were the same, the details seem to have different versions. The result was a much more careful scrutiny of weather forecasts country-wide rather than for NTS alone and the neighboring states. There was special emphasis on the northeastern quadrant.

These problems led to the development of one of the most used methods for measuring fallout around NTS, nationwide, and, before long, worldwide—a sticky paper that would retain its adhesiveness even when wet and could be spread out on trays about three feet above ground. The sticky paper could be gathered, folded into an envelope, and mailed to the New York Operations Office (later Health and Safety Laboratory) for analysis.

A picture of an early model of the sticky paper tray is shown in figure 12.12A, while one showing Dr. Eisenbud standing among an array of such trays is shown in figure 12.12B.

There was much more than this to the fallout surveillance network. Even at the time of the 1955 Congressional hearings, there was an extensive electronic and sticky-paper network with about ninety stations distributed throughout the United States. The sticky-paper technique remained in operation for many years, partly because of its simplicity and partly because the samples could be measured with laboratory instruments of greater sensitivity and ability to resolve the fallout into components than any field instruments of the day that could be left out in the weather. By 1955, the AEC laboratory in New York had assayed over two hundred thousand samples from the gummed films.

Incidents of high activities in snow or rain at points distant from NTS continued to multiply. These included Troy, New York, with an incidence of rain-out in a violent thunderstorm that will figure in later discussions; Chicago; Rochester (again); Salt Lake City (twice); and many smaller communities. Also, communities closer to the site began to report fallout *without* the intermediation of precipitation.

All of these were measured as external radiation dose rates. None of them presaged significant biological effects in the short term. Yet, the possibility of cumulative exposures through internal deposition and possible contamination of the food chain led to ever increasing concern and controversy. We will consider these presently.

FIGURE 12.12A. (Right) A latex-covered plastic film, 1-ft square on a stand 3 ft above the ground, collects falling dust, which adheres to the latex and is not removed by wind, rain, heat, or cold. Every twenty-four hours the film is changed; the exposed square is folded on itself, sealing adhesive portions together, and mailed to the AEC's Health and Safety Laboratory in New York for measurement. (Courtesy U.S. Congress 1955.)



FIGURE 12.12B. (Left) Dr. Eisenbud with an array of pans for catching fallout. The covers are latex-covered plastic film as described in figure 12.12A. (Courtesy of Eisenbud 1976.)

Just for the record, let it be noted that the rainout in Troy gave maximum readings of beta and gamma radiation of 120 mr/hr at 1 cm above the ground 2.1 days after arrival on the campus of Rensselaer Polytechnic Institute. Most of the readings were lower (Clark 1954). It was possible to make quite clear autoradiographs of the fission products adhering to an asphalt shingle and to a burdock leaf. Decay rates were between -1.26 and -1.52 as power functions of time. Also, the radioactive snows at Ann Arbor, Michigan (Meinke 1951), were carefully analyzed, and the radionuclides present were identified.

It appears that some of these contaminating events reflected the requirement by the military that studies of weapons effects be made at or just beneath the surface, as in the Buster-Jangle series (Hacker undated).

An important feature of the early test shots was the determination of fallout dynamics. This is an aspect of the research around nearly all weapons tests, but it was in the early Nevada tests that some of the most definitive measurements

could be made. Many of the shots were small enough to allow measurements over an area of manageable size, and there was considerable variety in the altitudes, methods of firing (balloon, air drop, high tower, low tower, surface, sub-surface), and differences in the devices themselves.

Much work was done on particle-size analyses and the effect of chemical composition. It soon became apparent that the distribution of fission products was not uniform over the particle-size range, that the radioactivity was frequently attached to larger nonradioactive particles,^(a) that fractionation of activity could take place in a fallout cloud, and that fallout at distant points might be quite different quantitatively from close-in, because of the different retention times of different particle-size distributions in the atmosphere. Furthermore, just as the work in the Pacific brought to light unknown currents in the ocean, the NTS work (along with the air work possible in the Pacific) revealed much about atmospheric mixing, stratification, etc. Indeed, it is said that Lester Machta confirmed the existence of the jet stream from measuring behavior of fallout in the atmosphere.

An early report from UCLA on Operation Jangle (Larson et al. 1952) showed that the average decay rate of fallout material for a surface detonation was significantly longer than from an underground detonation. In 1953, the characteristics of airborne radioactive materials from three of the Snapper shots were described. This work utilized high-volume air samplers for gross measurements and cascade impactors for particle-size analysis (Olafson et al. 1953).^(b)

Mean particle size for the longer-term airborne particles was less than $1\ \mu$, with 95% of the material smaller than $5\ \mu$. Decay rates were different for material from different shots. This particular material was only slightly soluble in water or dilute acid, and specific activity varied inversely with the radius of the particles. These findings indicate strongly that biological effects from fallout entering the body (i.e., as an internal emitter) could not be predicted reliably from measurements of external gamma or beta-gamma dose rates.

In 1954, a study of fallout phenomenology from Operation Upshot-Knothole allowed a discussion of surveys from 1951 to July 1953 (Lindberg et al. 1954). Among the findings was that in areas repeatedly contaminated over a two-year period, 90% of the residual activity was in the first inch of soil.

With particle sizes partly in the respirable range ($10\ \mu$ and below, see chapter 9), there was interest in whether or not inhalation of fallout either directly or via airborne dust could constitute a serious biological hazard. The UCLA group approached this possibility by an analysis of fallout materials from field operations and controlled inhalation studies in the laboratory (Taplin, Meredith, and Kade 1955). They used micropulverized fused insoluble materials from Area T-3 of NTS and also exposed animals (rabbits) to fallout materials by inhalation at stations located along two arcs, 7 and 106 mi from ground zero. They collected urine and tissue specimens and found that little or no radioactivity had entered by the inhalation route.

(a) The NRDL had already pointed this out for samples of fallout from Pacific tests.

(b) While this was a UCLA report, R. H. Wilson from Rochester and F. Lowman from the University of Washington are listed as collaborators. There was much interchange of laboratory personnel in NTS work of the 1950s, particularly to bring in specialists like Wilson on air sampling.

An important summary statement came in a UCLA report by Larson, Neel, and associates (1960). The abstract of this document is reproduced below:

Included in this report are summary statements of significant findings related to the distribution, characteristics, and biological availability of fallout debris originating from testing programs at the Nevada Test Site during the past decade.

The delineation of fallout patterns has been accomplished by the use of aerial and ground monitoring surveys. Only about 25 per cent of the total amount of fission products produced by tower-supported detonations was deposited within distances corresponding to fallout time of $H + 12$ hrs; very much less was deposited by balloon-supported detonations. Fallout particles less than 44 microns in diameter are presumed to be of greatest biological significance. About 30 per cent of the fallout radioactivity from tower-supported detonations was contained in the 0 to 44 micron particles as compared to almost 70 per cent for balloon-supported detonations. Fallout debris from balloon-supported detonations was also much more water and acid soluble than was the debris from tower-supported detonations. The <44 micron fallout particles contained a higher percentage of Sr89, -90 and Ru103, -106 than did larger sized particles, and there was a higher percentage of these radioelements in the particles from balloon-supported detonations. Within distances corresponding to $H + 12$ hours fallout time, balloon-supported detonations deposited a maximum of 0.13 per cent of the theoretical total Sr89 produced; tower-supported detonations deposited a maximum of 2 per cent. Tower-supported detonations also deposited a maximum of 7.2 per cent of the theoretical total amount of Sr90 produced. Beta decay curves approximated the $T^{-1.2}$ decay expression from $H + 12$ to $H + 6000$ hours; gamma decay curves deviated to the extent that irradiation doses calculated by the observed decay values were 1.5 to 2 times greater than those calculated by the $T^{-1.2}$ relationship.

Fallout radioactivity is apparently confined to the first 2 inches of the soil surface unless the surface had been mechanically disturbed. Most of the fallout debris that was redistributed by various environmental factors after original deposition consisted of particles less than 44 microns in diameter; the particles in this size range also represented the predominant contamination on plant foliage. Sr90 levels in surface soil ranged from 31.9 to 142 mc/sq. mile in virgin areas near known fallout pattern midlines and from 7.5 to 22.7 mc/sq. mile in agricultural areas which did not necessarily coincide with fallout pattern midlines. The accumulation of radioiodine by native animals was observed to be a function of distance from Ground Zero. Radiobarium-140, Y-91, Sr89 and Sr90 were major bone contaminants. Post-series sampling of native animals indicated that the accumulation of Sr89 was also a function of distance from the point of detonation; however, the Sr90 accumulation by animals correlated poorly with the strontium unit levels in soils. The strontium unit levels increased in milk immediately following contamination of the farm with fallout debris, and then decreased with time as well as the amount of Sr associated with the cattle's diet.

Observations during the past decade indicate that less than 10 per cent of the total Sr produced from nuclear detonations at Nevada Test Site has been deposited within 200 miles from the point of detonation.

The alleged discontinuity in behavior of particles larger or smaller than 44 μ has become something of a generalization for all of the NTS studies. It has obvious implications for biological availability.

For further particle-size considerations, we turn to a report to the Test Director of Operation Teapot for the Civil Effects Test Group (Barmash et al. 1958). A study was made of particle sizes as a function of distance from ground zero. Obviously, much of the material in the initial cloud is relatively large and drops out soon. For example, this work found that particles larger than 100 μ were present but decreased rapidly with distance from ground zero. By contrast,

smaller particles do not necessarily decrease; they may even increase with distance out as far as two hundred miles. Furthermore, the smaller-sized material tended to be more soluble.

A compact summary-type statement regarding the UCLA work was presented by Larson at the First National Radioecology Symposium (chapter 11) held in 1961 and published in 1963. Larson (1963) gives a review first of the Trinity site resurveys, followed by a summary of the characteristics and measurements of fallout from NTS operations. He underscores the importance of knowing as much as possible of what goes on in the first few minutes after a detonation to understand and predict subsequent behavior of the fallout and its potential for biological effects. He reviews the particle-size information and radiochemical findings for several types of shots and gives the kiloton yields in each. Also, he gives estimates of the total curies of ^{89}Sr produced (27,350,000), deposited at $H + 12$ hours (285,300) and available for deposition elsewhere (27,064,700). For ^{90}Sr , the comparable figures are 162,485; 8,066; and 154,419. Solubility in water and 0.1 normal HCl was considerably greater for the balloon than for the tower shots.

UCLA was not the only laboratory involved in this work, of course. The military had extensive cloud sampling and air sampling activities, as did Sandia Laboratories, Los Alamos, and Livermore. However, these were more oriented toward weapons behavior and of less pertinence to biomedical evaluations.

The U.S. Weather Bureau played an important role. Useful summaries appear in the Congressional hearings. One report that gives a clear idea of just how the information was gathered concerns the North American fallout from Operation Teapot (List 1956). This work involved collaboration with the Radiological Physics Division at Argonne National Laboratory and elsewhere. The work is full of fallout distribution maps, autoradiographs of rain collection, and details of the gummed film network.

The New York Operations Office of AEC prepared a general and historically oriented dissertation emphasizing data from the tests of spring 1952. They compared airborne with settled dust and emphasized that the magnitude of the depositions was minute, especially when compared to the natural radioactivity of the earth's surface and atmosphere (Eisenbud and Harley 1953). Only close-in "hot spots" had levels of real biological concern at the time.

An addition to the methodology was described by Romney et al. at UCLA (1959). This was a granular collector with a removable mylar plastic liner in a tray filled with polyethylene plastic granules $1/8$ to $3/16$ in. in diameter. It was used extensively in the 1957 series (Operation Plumbbob). Its particular advantage was ease of separation of primary fallout particles for physical and chemical characterization.

What does all of this have to do with biology and medicine? Why should the AEC Division of Biology and Medicine and the PHS expend resources and personnel on measuring and characterizing fallout? Obviously, the first job is to find where it went and seek out any areas of potential danger to humans and to the environmental fauna and flora. The second job is to understand enough about the relationships involved to be able to correlate something readily measured (external beta-gamma or gamma dose rates) to effects from the fallout on body surfaces and after internal deposition. Third, the persistence and characteristics over time are essential to know if long-term possible doses and effects are to be predicted. We will examine some of the first returns in biology in the next section.

C. The Early Biological Information from NTS

The UCLA people produced the bulk of the onsite and near offsite biological information in the early years. In a report on Operation Upshot-Knothole, Lindberg et al. (1954) describe radioecological surveys that had been in progress intermittently from September 1951 through July 1953. Samples of native soils, plants, and animals before, during, and after the test series over distances out to 30 mi from ground zero suggest that microcurie-levels of radionuclides (not specified) are available for absorption and metabolism by grazing animals. They found amounts in femurs and livers of jack rabbits threefold higher than in 1951, while the amounts associated with plant materials were increased by a factor of two. Ingestion, rather than inhalation, is given as the primary intake route. In a comparable report by Lindberg et al. (1959) concerning Operation Teapot in 1955, the role of particle size in plant contamination (the 44- μ phenomenon) is fully described, along with the solubility of the material on plant foliage (only 6% to 21% in 0.1 N HCl). Tissue burdens in animals decreased with distance from ground zero much the same as the plant contamination. Interestingly, the beta activity in rabbit femurs tended to remain fairly constant to as far out as 140 mi.

Amounts of iodine in thyroid are first mentioned in this report. The thyroid burden at 60 mi from ground zero was higher than at either 10 or 140 mi. They attributed the thyroid activity to ^{131}I .

Importantly, the gross tissue burdens in animals were more or less proportional to the contents of the gastrointestinal tract, suggesting again that ingestion rather than inhalation accounted for the tissue contents.^(a)

Because plants are selective collectors for the small particles, and the small particle concentrations in the fallout remain more or less constant with distance for many miles, the amount of bomb debris in grazing animals tended to be independent also of total fallout. Details for other similar surveys can be found in the annual reports and in more compact and available form in the monumental summary prepared by Larson et al., Director of Program 37 of Operation Plumbbob (Larson et al. 1966). While this test series took place in 1957, it required several years to measure all of the samples in the laboratory, get the report declassified, and correlate with earlier years. The report reiterates the facts already quite evident, viz., chronic tissue burdens in animals do not correlate well with measured external dose rates of environmental contamination, nor does the activity associated with plant materials. Assimilation of specific fission products by animals is highly variable. In addition to the finding on radioiodine mentioned above, the body burden of radiostrontium in desert rodents six months following the fallout event was about five times greater at 130 mi than at six other locations ranging from 40 to 400 mi from ground zero. This was for Operation Teapot. For Operation Upshot-Knothole, the body burdens in native rodents at 130 mi were seven times higher than on the test site. Furthermore, the ratio of ^{89}Sr and ^{90}Sr was variable, which suggests some fractionation phenomena even for these closely related isotopes, based perhaps on particle-size phenomena.^(b)

(a) Undoubtedly, this reasoning underlay the conclusion in the earlier report also.

(b) Remember there are differences in the chain from ^{89}Kr to ^{89}Sr versus ^{90}Kr to ^{90}Sr that could result in attachment to different particle distributions.

Despite the apparent complexities described above, a broad view of the biological availability showed reasonably consistent patterns. Note the following from the summary of chapter 7 from the Operation Plumbbob report:

1. The data presented are representative of the relative fission product accumulations in adult animal population of the species studied within an overall factor of two.
 2. Comparison of the biotic data from five different detonations shows a marked similarity in the pattern of mixed fission product accumulation (total beta activity) in animal tissues. The similarity is apparent when the data are related to the time at which fallout occurred. Total activity in tissues tended to decrease as the fallout time-of-arrival increased.
 3. The rate at which the total beta activity in tissues decreased with increasing time of fallout was slightly greater for the balloon supported Shot Priscilla than for four tower supported detonations and correlated with differences in the amount of the less than 44 micron fallout material that was deposited.
 4. For comparable locations within the two fallout patterns (Priscilla and Smoky), the amount and kinds of radionuclides present in bone samples were similar despite differences of orders of magnitude in the amount of fallout deposited by the two shots. This similarity can be accounted for by the relatively higher solubility of the Priscilla fallout material.
 5. Biological "hot spots" were identified with Boltzmann (78 miles from ground zero), Diablo (60 miles from ground zero), and Shasta (172 miles from ground zero) fallout patterns. The degree of biological accumulation in the Boltzmann and Diablo hot spots reflected the heavy deposition of fallout, particularly of the less than 44 micron fraction, in these areas. However, high values occurred in animal tissues sampled from a Shasta location even though dose rates obtained by ground and air monitoring failed to reveal correspondingly high levels of deposited radioactive debris in that area. Other animal tissues sampled from the Shasta radiological hot spot did not show high fission product concentrations.
 6. Apart from the exceptions shown by comparison of the tower-supported Shot Smoky and balloon-supported Shot Priscilla, the pattern of biological accumulation of beta activity appears to be similar for the detonations studied during the Plumbbob, Teapot, and Upshot/Knothole Test Series.
 7. Jackrabbit bone levels of Sr^{90} from animals in Station VI Area were about the same in 1958 as in 1957. There was an increase reflected in 1959, followed by a decrease to the 1957-58 levels in 1960, and an abrupt drop in 1961, i.e., from 25 to 10 pc $\text{Sr}^{90}/\text{gm Ca}$. This occurred despite the apparent constant level of Sr^{90} in soil.
 8. Data suggest that the higher levels of Sr^{90} in the indigenous animals are associated with animals which were living in the early sequence of contamination, i.e., during and immediately after fallout, rather than with animals that were born later and merely lived in the contaminated environment.
- (Larson et al. 1966)

The chapter is full of tables and graphs and potential correlations. However, the variability of the observations, which the authors note, is such that only broad trends can be considered along with some interesting sidelights. For example, there is less ^{90}Sr in the bones of kangaroo rats than in jack rabbits, probably because of differences in living habits. All of the levels recorded, given in picocuries or strontium units (pCi/g Ca, see section on global fallout), are far too low to presage any eventual biological effects. This work is thus pertinent largely to the question of biological availability.

A detailed published work on ^{90}Sr in the kangaroo rat and jack rabbit shows several points of interest (Neel and Larson 1963). The relation between soil concentration and strontium in bone was investigated in animals of Area I, a

relatively close-in area 13 mi from the NTS center. Operation Buster-Jangle raised soil levels of ^{90}Sr in this area by approximately a factor of ten, and a subsequent shot added more. The bone content rose to 33 strontium units (section VI B) by fall 1952. Despite additions from other shots that brought the soil concentrations to double or more, the bone content decreased with time. It went up by a factor of two during the Plumbbob series, even though the average measured soil content remained essentially constant. Only after the Kiwi shot in 1959 (see chapter 14) did the bone levels reach above those seen in 1951. They went back down in 1960 and further down in 1961. The movement of fallout isotopes, even in a desert ecosystem, clearly is not simple.

It happens that Neel and Larson got many samples close to the Smoky tower shot in 1958, as well as some as far out as 432 mi. Since this shot has assumed great importance in the recent retrospective analyses, the table from Neel and Larson showing the ^{90}Sr in soil and in jack rabbit bones in 1958 and 1959 is reproduced as table 12.8.

TABLE 12.8. 1958 Strontium-90 Soil Levels and 1958 and 1959 Jack Rabbit Bone Levels at Various Sampling Sites in Nevada and Utah

Distance from Nevada Test Site (mi)	Sampling Area	Strontium-90 Levels					
		Soil (millicuries per square mile)		Bone (strontium units)(a)			
		1958		1958		1959	
		Sample Size	Average ¹	Sample Size	Average ¹	Sample Size	Average ¹
0	Smoky Tower	10	9014 ± 282	5	50.4 ± 10.5	6	43.2 ± 5.9
20	Area I, Nevada	12	513 ± 33	2	19.0 ± 0.8	5	63.1 ± 14.9
74	Moapa, Nevada	10	16.3 ± 2.6	6	13.8 ± 2.6	11	18.0 ± 2.1
76	Delamar, Nevada	10	22.9 ± 0.9	5	14.6 ± 2.1	7	17.1 ± 1.6
80	Warm Springs, Nevada	10	92.6 ± 8.7	5	26.8 ± 4.0	6	30.0 ± 7.3
82	Glen Rox, Nevada	10	142 ± 22	4	21.8 ± 1.4	1	19.6
96	Overton, Nevada	1	21.0	1	15.5	9	13.9 ± 1.4
132	Belmont, Nevada	10	32.4 ± 1.6	10	23.8 ± 1.5	10	28.0 ± 3.2
135	St. George, Utah	10	45.6 ± 2.8	5	19.6 ± 0.6	5	25.3 ± 4.7
136	Enterprise, Utah	10	41.2 ± 1.9	7	13.7 ± 0.9	8	19.3 ± 3.2
232	Clear Lake, Utah	10	25.9 ± 0.8	5	11.1 ± 1.3	9	18.5 ± 3.5
235	Antimony, Utah	6	29.0 ± 1.9	4	16.2 ± 3.2	6	17.3 ± 3.9
240	Antimony-Otter Creek, Utah	10	43.5 ± 4.0	6	15.0 ± 2.8	9	15.4 ± 1.6
270	Fremont, Utah	10	26.1 ± 1.2	5	17.4 ± 1.8	6	14.2 ± 1.6
272	Reno-Sparks, Nevada	12	16.4 ± 1.0	4	27.3 ± 3.8	9	19.0 ± 2.2
300	Fountain Green, Utah	10	37.6 ± 2.2	6	13.3 ± 0.4	8	22.4 ± 1.8
356	Columbia, Utah	10	67.2 ± 2.2	5	20.6 ± 1.0	9	20.7 ± 1.4
432	Vernal, Utah	10	13.8 ± 1.6	5	11.9 ± 1.6	8	12.9 ± 1.4

¹Average ± one standard error of the mean.

(a) pCi/gm Ca. See section on global fallout.

Source: Modified slightly from Neel and Larson 1963. Reprinted with permission of Van Nostrand Reinhold Co., Inc., New York, copyright 1963.

The most obvious generalization is not to predict body or bone burden except in the most general way directly from fallout measurements. Also, it bespeaks the virtues of having some direct measurements on biological materials in hand—not an easy assignment for contamination of such large areas.

Marvin Van Dilla, who was instrumental in the development of gamma-ray spectral analysis at Los Alamos, brought the technique to bear on analyses of rumen contents and tissues from cattle grazing in the vicinity of NTS (Van Dilla 1959). The purpose was to check on gastrointestinal absorption of the several isotopes (Langham 1960). He found a predominance of cerium, ruthenium, and $^{95}\text{Zr}/^{95}\text{Nb}$ in the food ingested by the animals, while ^{137}Cs was below detection limits. Yet, the liver and muscle showed a prominent ^{137}Cs peak, plus a trace of $^{95}\text{Zr}/^{95}\text{Nb}$. Cerium and ruthenium were below the limit of detection in the tissues, even though they predominated in the rumen. Thus, many of the radionuclides present from fallout in the environment must be quite insoluble and poorly absorbed. Their presence alone in the environment or even in the food does not necessarily gauge hazard on ingestion. Some of the data are shown in table 12.9.

TABLE 12.9. Radionuclides in Cattle Grazing in the Vicinity of the Nevada Test Site (1958-1959)

Sample ^a	$\mu\text{mc/kg}$					
	Cs^{137}	Zn^{65}	Zr^{95}	Nb^{95}	Ru-Rh	Ce-Pr
Liver (KC)	920	174	trace
Muscle (DV)	1,160	224
Rumen, av (DV)	5.8×10^4	12×10^4	0.26×10^4	4.3×10^4
Rumen, av (NTS)	22×10^4	44×10^4	1.4×10^4	14×10^4
Rumen, av (KC)	2.3×10^4	4.6×10^4	0.17×10^4	3.1×10^4

^a DV and NTS herds near Nevada Test Site; KC herd from Nevada-Idaho border, about 300 miles north. Rumen refers to rumen contents.

Source: Reset from Langham 1960. Reprinted with permission of University of Minnesota-Twin Cities, Minneapolis, Minnesota, copyright 1960.

An indication of some of the more complex and experimental, rather than purely observational studies in connection with the Nevada tests, is seen in some work done in Project 2.7 of Operation Jangle. Smith, Boddy, and Goldman (1952) went to NTS from the NIH to conduct two biological experiments, one for a surface test and one for an underground detonation. The primary purpose was to assess the hazard due to inhalation of dust and to compare the external and internal doses in exposed test animals. These were placed at 2,500; 5,000; and 8,000 ft from ground zero on arcs. Animals were sacrificed at H + 10 to H + 24 hr, at D + 2, + 4, + 9, and + 70 days. Homogenates of lung, liver, spleen, kidney, blood, bone, urine, and gut contents were dry ashed for measurement of radioactivity, and samples of soft tissue were prepared for autoradiography. The NIH workers measured external dose with National Bureau of Standards (NBS) film dosimeters both at the surface and in foxholes in which some of the animals were placed. The internal doses were determined by calculation from

the tissue contents. The external gamma doses from the surface test were less than 10 r^(a) at all positions on the 5,000- and 8,000-ft arcs. The doses along the 2,500-ft arc ranged from 265 to 300 r. External gamma doses from the underground test were considerably higher.

As a function of organ and time, radioactivity in tissues from all animals exposed during the surface shot ranged quite low, from 0.06 to 2.13 μ Ci, while those from the underground test ranged from 2.22 to 31.1 μ Ci. Integrated doses to the lungs given in rep^(b) were from 0.19 to 8.83 rep. The radioactivities fell off rapidly with time and were below the limits of detection by D + 9. The conclusion was that internal contamination from inhalation and/or ingestion was not significant compared to the external doses received under the conditions of Operation Jangle.

This conclusion is for the short term. The autoradiographs of lung tissue showed three distinct types of radioactive particles: a pure alpha emitter, probably ^{239}Pu ; a particle with mixed alpha and beta radiations; and one emitting only beta particles. Since the experiment was short-term, no information was gathered regarding long-term doses or possible effects. However, a significant lifetime dose could be envisaged from particles like the plutonium in the lungs, if it were relatively insoluble and became fixed.

A further study of lung dose came from the New York Operations Office (Blatz and Solon 1953). This was a calculation of potential lung dose to humans from measurements made on radioactive airborne dust collected near ground level at about 275 mi from NTS in fall 1951. Using the specific activity at the point of collection as a function of time after the explosion (not identified), an integral dose to infinity of about 17 mrep was calculated, an inconsequential dose physiologically.

Taplin, Meredith, and Kade (1955) evaluated the possible inhalation hazard by analysis of results from field operations and parallel controlled inhalation studies in the laboratory. This work came from UCLA.

Detection and quantitation of fallout particles in lung, based on a lung excised from a diabetic in March 1963, came from work at the University of Michigan School of Public Health (Wegst, Pelletier, and Whipple 1964). They were interested in finding and identifying single particles. They found four in the removed lung (right), but total activity in areas of the lung in which particles were not identified was not greatly different. Thus, only a portion of the lung activity came from identifiable particles. (They analyzed for ^{141}Ce , ^{144}Ce + ^{144}Pr ; ^{103}Ru , ^{105}Ru + ^{106}Ru ; ^{95}Zr + ^{95}Nb ; and ^{40}K .) Doses were negligibly small.

One of the few truly ecological studies of this early period concentrated on Frenchman's Flat and Jackass Flats, where the majority of the tests occurred (Allred and Beck, 1963). Since there was no satisfactory investigation of the flora and fauna of the area before the tests, the study has many problems. The NTS appears to be on the border between the Great Basin and the Mohave Desert ecosystems and, therefore, only small changes in locale make enough difference that simple comparison to adjacent areas could not serve as an adequate control. The findings are summarized by the following:

(a) This work was done when the abbreviation for roentgen was r rather than R. We use the terminology used by the investigators.

(b) Roentgen equivalent physical, an early term that can be equated roughly to the rad for present purposes (see chapter 16).

1. There is a relatively rich fauna despite appearances to the contrary.
2. Destruction of plant communities was quite evident.
3. Insects and other invertebrates showed more species inside the disturbed areas than outside, while mammals did not show this effect, except that their ranges seemed to have been extended. (Transient increases in certain groups in a disturbed area seem to be moderately well known.)
4. More work is needed simply to classify the forms found, particularly the invertebrates, since many unidentified species were found.

These examples give the flavor of those early biological programs conducted at NTS that have a bearing on the role of radioactive materials deposited in the body. Much that concerned only external dose has been omitted, especially the large programs looking for the effects of neutrons and neutrons with gammas. In comparison with some of the extensive plans that involved much more genetic work and very large numbers of animals, the amount of such work seems rather sparse. However, much was being done or about to be done concerning offsite exposures at from moderate to considerable distances and on the contamination of food supplies. This will concern us in the following sections.

D. Offsite Exposures Near NTS

In this section, we will use the term "offsite" to connote exposures within a few hundred to a thousand miles of NTS and exposures linked to specific events at the site. We are not including here continental fallout or global fallout, even though the source of these may have been in part operations at NTS. These are better discussed as separate entities (section VI).

1. People—Phase I

a. The Background

It is obvious from what was presented in sections B and C of this part that the presence of fallout measured either at the time or retrospectively by analysis of soils or of plants and animals could be demonstrated several hundred miles from NTS.^(a) We have said nothing yet about possible involvement of human communities in these events, and it is time we did.

The prevailing winds at NTS are out of the southwest with frequent shifts to south or west and occasional vectors from north quadrants. As a result, the fallout clouds moved mostly north and northeast from the site, occasionally east, or on rare occasions, southeast or south. The most involved communities were to the north and northeast of NTS in Nevada and Utah, but Idaho and Montana were also favored on occasion. Saint George and the rest of Washington County in Utah; Salt Lake City and surrounding communities; and various communities, mostly small, in Nevada have been featured most frequently in the investigations. Some typical trajectories of fallout from NTS detonations are shown in figure 12.13. These pertain to shots in 1962 but can serve as examples of typical behavior.

(a) In addition to the UCLA, AEC, and PHS work already cited, further details can be found in Dunning (1958, 1959), Klement (1965), and in the Congressional hearings already cited.

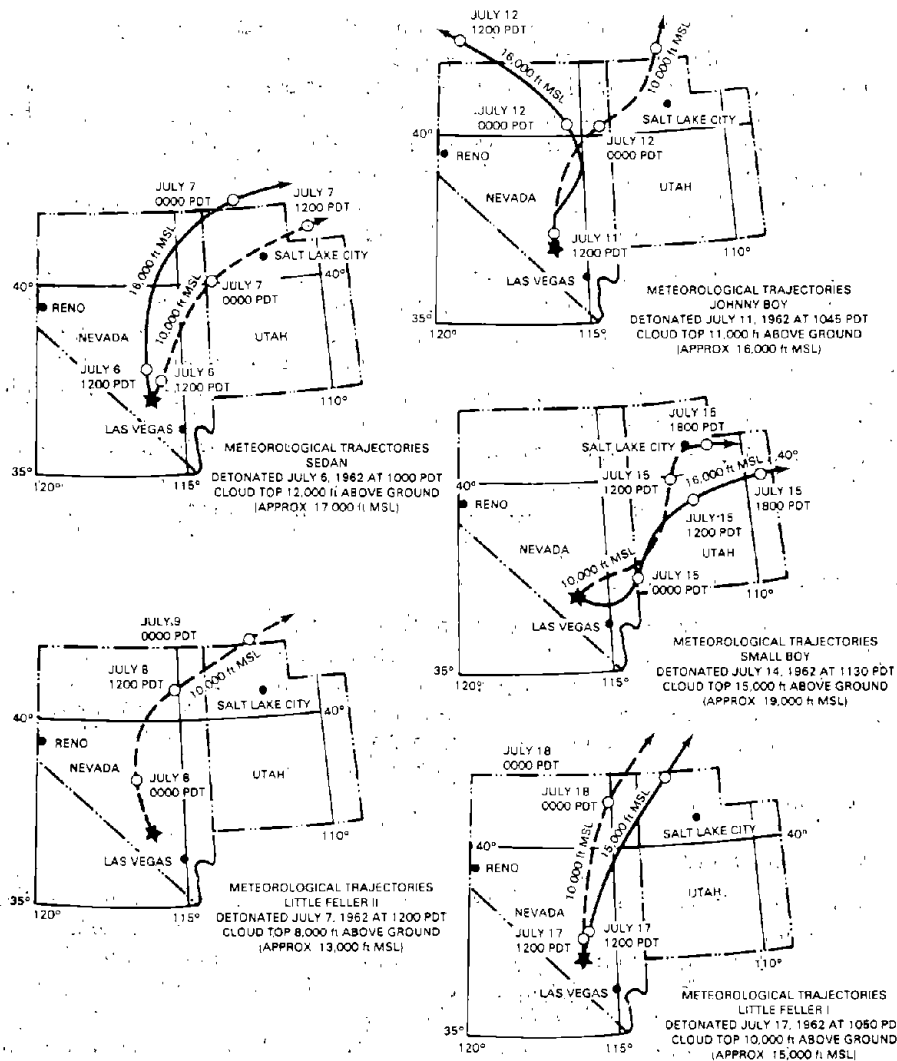


FIGURE 12.13. Typical trajectories of fallout from Nevada Test Site detonations. The line purports to describe the path of the cloud center. There was, of course, some lateral spread, particularly as time passed. (Redrawn from Mächta 1963. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1963.)

The evaluation of dose and thus of hazard depended in the early 1950s primarily upon the film badge, other measurements of the external gamma or beta-gamma radiation doses, and of gross radioactivity measured in air and in water. These were found to be well within limits set by AEC and later by the Federal Radiation Council (FRC) for population exposures. Details, voluminous

for external gamma radiation, are given for the early to mid-1950s by Dunning (1958).^(a) Following the dictum that if the external dose was below limits the dose from deposited radionuclides would be negligible and the finding of very low quantities in water, both the exposed population and the monitoring teams mostly decided that all was well (or, at least, not bad). Remember that gamma spectrometry only came into its own about 1958, and, before that, identification of individual radionuclides required laborious radiochemical procedures not at all applicable to field determinations. Iodine became the cause célèbre.^(b) As Eisenbud and Wrenn (1963, p. 1134) remarked in connection with the measurement of iodine, "neither the proper tools for measurements nor the prerequisite interest existed" for the prior tests.

The results of the experimental laboratory work with animals described in earlier chapters showed more and more clearly that even low levels of exposure to certain radionuclides might have very real biological effects, and the fever of activity grew for the measuring of specific isotopes in all fallout. The presence of the three-year moratorium on testing made it possible to go back around the test site and analyze for the deposited fallout at leisure and in more depth, especially to look for cesium and strontium, which had reasonably long half-lives. The results indicated a few instances of high cesium concentrations and a few instances where the strontium concentrations might have originally approached undesirable levels.

It was the participation of the food chain and particularly the iodine-foilage-cow-milk-human sequence that led finally to serious concerns in and about the communities treated to large and successive doses of fallout from NTS. The trigger was measurements of iodine isotopes in the fallout, on foliage, in water and food, and in the thyroid gland of humans and animals from tests occurring after the moratorium had been lifted. (Unfortunately, none of the iodine from the earlier tests was left to measure, so cumulative doses could only be guessed at.) We will review the iodine story as representative of the approaches taken. Measurements of fallout iodine in thyroids started, of course, well before this time. Remember Windscale (chapter 11)? Van Middlesworth (1956), formerly of Berkeley and then at the University of Tennessee in Memphis, was probably the first to report iodine from continental and global fallout in cattle and sheep of the United States. Also, White and Jones from Berkeley (1956) showed uptake of ^{131}I by human and bovine thyroids (151 human and 1,000 beef thyroids) gathered in northern California and assayed between October 1955 and October 1956. The thyroid burden of ^{131}I in the humans was much lower than in the cattle. (More in section VI.)

b. University of Utah and Utah State Work

As for Windscale and the Pacific Proving Ground, it was the thyroid of the child that appeared most vulnerable because of its small size and rapid uptake of radioiodine. By July 1962, the sampling of fallout had become more sophisticated locally as well as nationwide. It happened that the University of Utah

(a) This summarizes extensive offsite monitoring activities by the PHS group under Oliver Placak and UCLA data collected by Kermit Larson, augmented by work from H-Division of Los Alamos and the AEC Health and Safety Laboratory in New York.

(b) Yes, iodine again, just as at Windscale and at the Pacific Proving Grounds!

people were engaged in a statewide radiological ecology study in cooperation with the Utah State Health Department. On July 7, 1962, Pendleton was in the field about twenty miles from Salt Lake City with a group of students measuring background radiation. A dusty cloud was observed, and when it arrived the radiation levels went to one hundred times normal background (i.e., to 2 mr/hr) (Pendleton et al. 1963). The State Health Department measurements on the next day showed gross airborne beta activity of 900 pCi/m³. This galvanized a very active collection of milk samples^(a) and analysis, especially for ¹³¹I. Thirty-nine dairy farms around Salt Lake City were sampled, and external counting of thyroids in humans on these same farms was initiated in August.^(b)

The ¹³¹I content of these milk samples varied from 0 to 800,000 pCi/l. This variation was due partly to location (these fallout clouds could be quite limited in extent) but was due mostly to feeding practices at the time. The maxima were in the milk obtained from cows feeding on fresh green forage or in wet meadows. The minima were in those cows that happened to be on stored feed at the time.

There were a total of seventy-six stations, and the ¹³¹I intake of persons drinking one liter of milk per day from a given station was calculated. The thyroid and total body counting work gave similar wide variations. The dairy families counted in August showed the amounts in thyroid given in table 12.10.

The radiation doses associated with these amounts were calculated by Pendleton et al. (1963), but only one was given officially. This was for the peak uptake of 800,000 pCi. The associated dose was 14 rad assuming an uptake of 30% by the thyroid, an effective retention time of 7.6 days and a thyroid weight of 2 g.^(c) This was, of course, an infant.

The possible thyroid doses were expanded upon a bit by Pendleton, Lloyd, and Mays (1963) in a paper published in *Science*. A thyroid dose of 1 rad would be expected for infants averaging 58,000 pCi; the adult dose would be about one-tenth that of the infant dose under the same conditions.

These doses are, of course, not in the same class with those to the Marshallese (section III D 2) or probably those from the Windscale event. Yet, the maximum of 14 rad was well above the 0.5 rad of the RPG. Even the average infant dose of 1 rad was twice the Guide. The chief cause for concern was the fact that about 53,000 Utah children may have been exposed to the 1962 releases. How many? We will have to return to that question.

Pendleton et al. (1963) attempted to get some sort of cumulative dose estimation over the period of the Nevada tests. Since there were no data for milk in the area of concern prior to 1962, and none for iodine in soils, they fell back on

(a) A milk collection network was, of course, already in operation for global fallout (see section VI).

(b) It was thought that the incident described represented fallout from the Sedan shot on July 6. Others came in rapid succession, however, up to July 17 so that thyroid iodine content could not be ascribed to any single event. Furthermore, as Mays described in the 1963 Congressional hearings at which the same biomedical data were presented, the beta activity from the Sedan shot was not from fission products but from tungsten activated by neutrons. However, there were many other events that might have contributed ample ¹³¹I. There was no question that the peak in activity was ¹³¹I.

(c) In later Congressional hearings on this same work, Mays (1963) gave an average infant dose of 1 rad.

TABLE 12.10. I^{131} in Utah Dairy Families Measured by Thyroid Counting and Total Body Counting

Person	Sex	Age	I. Milk/Day	Day Counted	pc I^{131}	Per Cent Uptake*
9-a	M	19	3.0	1 Aug 62	11,000	8
9-a				22 Aug 62	2,900	8†
9-b	F	11	0.7	1 Aug 62	6,300	19
10-a	F	7	0.7	2 Aug 62	4,100	26
10-b	M	5	1.1	2 Aug 62	4,200	17
10-c	M	30	2.1	2 Aug 62	7,600	16
10-d	F	26	0.5	24 Aug 62	760	28†
31-a	F	11	0.8	1 Aug 62	7,800	19
31-a				24 Aug 62	2,200	23†
31-b	F	8	0.8	1 Aug 62	10,200	24
31-b				24 Aug 62	1,800	19†
31-c	F	4	0.5	1 Aug 62	4,000	15
31-d	M	35	1.0	1 Aug 62	3,600	7
32-a	M	10	1.5	6 Aug 62	4,900	9
32-b	F	14	4.0	6 Aug 62	7,800	5
32-b				22 Aug 62	3,600	7†
32-c	F	13	1.7	6 Aug 62	4,200	7
32-d	M	41	1.7	6 Aug 62	3,700	6
32-e	M	9	1.7	6 Aug 62	4,100	6
32-f	F	45	1.0	22 Aug 62	710	5†
57-a	M	61	1.0	25 Aug 62	2,800	9†
57-b	F	49	1.0	25 Aug 62	3,000	10†
59-a	M	48	0.5	25 Aug 62	4,200	46†
59-b	F	13	0.7	25 Aug 62	2,200	18†
60-a	M	27	2.0	31 Aug 62	10,900	14†
60-b	F	16	1.0	31 Aug 62	8,700	23†
63-a	F	41	1.0	29 Aug 62	2,400	34†
63-b	M	42	1.0	29 Aug 62	3,400	47†
Average						17

* Ratio of that measured in the body to that computed for 100 per cent uptake from milk.

† These numbers represent whole body counts.

Source: Reset from Pendleton et al. 1963, and Pendleton, Mays, and Lloyd 1963. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1963.

an estimate based on the gross beta-particle measurements made in air (Dunning 1958 and the Utah State Department of Health). With many assumptions and normalization of the air figures to the 1962 data, they came up with the possible doses to thyroid given in table 12.11. These were expanded upon in the Congressional hearings to give estimates calculated from the yield as well as from the air measurements.

TABLE 12.11. Estimated Radioiodine Doses to Thyroids from Fallout in Utah from Several Nevada Tests

Explosion Dates	24-hr Av. Air β Concen.	Est. Av. Infant Thyroid Dose	Number of Exposed Children Under 2 Years	Air Sampler Location
7 May, 1952	20,000 pc/m ³	6 rad.	41,000	Ogden, Utah
19 May, 1953	287,000	84	700	St. George
15 July, 1957	2,900	0.9	47,000	Salt Lake City
18 Aug, 1957	3,200	0.9	47,000	Salt Lake City
16 Sept, 1957	8,600	2.5	47,000	Salt Lake City
July, 1962	3,400	1.0	53,000	Salt Lake City

Source: Modified slightly from Pendleton et al. 1963. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1963.

It was recommended that any farm in the Utah group with milk averaging over 1,000 pCi of ¹³¹I per liter of milk^(a) should put their cows on stored feed and that the milk should be diverted to cheese making, etc. which allows time for radioactive decay.

It appeared that heavier contaminations may have occurred in earlier years, and the average cumulative dose to an infant in 1953 might have been as much as 84 rad (table 12.11). But we must make many assumptions regarding the ¹³¹I content of these clouds. (This one was in St. George, Utah, not Salt Lake City. The pretty town of St. George got more than its share of NTS fallout.) On the basis of such figures and the moderately large population at risk, many people concluded that these exposures warranted a medical survey for thyroid nodularities and other thyroid dysfunctions.

c. The Knapp Study

Harold A. Knapp, a former employee of the AEC (Fallout Studies Branch, Division of Biology and Medicine), but by the time of the 1963 hearings on the staff of the Institute for Defense Analysis in Washington, presented a report calculating ¹³¹I in fresh milk and human thyroids following a single deposition of nuclear-test fallout (Knapp 1963). This document appears to have been prepared specifically for the hearings. It was based on the accumulated data from many sources. It concentrated on the fallout from the Small Boy shot in July 1962 but bore also on the findings of Pritchard, Mays, Lloyd, et al. at the University of Utah, which may have involved other shots as well. The Knapp report includes both calculated and observed levels of radioiodine in thyroids for persons in exposed families in Utah, albeit taken from different sources. It was a detailed analytical discussion with many cross-checks and comparisons of different computational schemes. The conclusions, summarized below, were drawn, we emphasize, from measurements that were not initially intended to investigate the relation between ¹³¹I levels in milk and the external gamma levels from fallout on the ground.

(a) The figure chosen by the FRC (see section VII) for the RPG was 100 pCi/l (bottom of Range III), but this applied to longer-term exposure.

1. Levels in fresh milk reach a maximum in four days and thereafter decrease exponentially with a half-time of five days.
2. The maximum level in fresh milk in μCi (pCi) ^{131}I per liter (I_{max}) showed ratios to the external gamma dose rate at $H+24$ hr measured in mr/r (r_0), ranging from 26,000 to 100,000 (i.e., I_{max}/r_0). If broader assumptions are made, the ratio ranged from 18,000 to 220,000. These are best estimates for a series of communities from fifty to four hundred miles from ground zero.
3. A model was developed for estimating the ^{131}I content of the human thyroid and the radiation dose resulting from daily consumption of fresh milk from cows grazing on a pasture on which there had been a single deposition of fallout.
4. Calculated thyroid burdens in people on dairy farms in northeast Utah based upon measured levels of ^{131}I in milk were compared with in-vivo measurements. The calculated burdens ranged from one to three times the measured burdens, using an assumed consumption of one liter of milk per day. Calculations based on the individual's own estimate of intake did not correlate well at all with measured quantities.
5. On the basis of all this, the thyroid dose due to ^{131}I deposited from a single event was compared with the calculated lifetime whole-body dose due to external gamma radiation from the same fallout. For a one-year-old child, the internal dose to the thyroid could be from 60 to 240 times the external gamma dose, if the calculations were correct.
6. Furthermore, the calculations indicated that milk levels of from 1,000 to 5,000 μCi of ^{131}I per liter could develop when the external gamma levels from the fallout were too low to be distinguished from natural background using ordinary field-survey methods.^(a)

Knapp's report is supported by data from many quarters. Of particular interest are derivations of the kinetics of ^{131}I in milk from the Windscale accident (Booker 1958; Garner 1960) compared to those from the Nevada-Utah field conditions. (They were surprisingly similar considering the large differences in conditions.) The applicability to the shots other than Small Boy is examined, along with the role of particle size, etc. There are a total of eight appendices to the Knapp document.

To go further would be beyond our scope. However, we should pause to state that this report was subject to an exhaustive review by an ad hoc committee of the Joint Committee on Atomic Energy of the U.S. Congress. Members were: Cyril Comar, Cornell; John Gofman, Lawrence Livermore; Wright Langham, Los Alamos (Chairman); Julian Nielsen, Hanford; and Oliver Placak, PHS Southwestern Regional Health Laboratory. The chief problems raised were the uncertainty of the field measurements, and thus of r_0 and the extent to which this variability had been accommodated by the author. The resulting instability of the derived figures, the fact that different sets of data of different origin had to be used for the two prime parameters under discussion, the fact that the only checks on the thyroid activity calculations were measurements

(a) Before we get too excited, let us remember that 5,000 pCi is only 0.005 μCi and that the yearly RPG for the general population (children are the critical group) is 36,500 pCi of ^{131}I or 0.037 μCi . If taken for a year at 5,000 pCi/l , the RPG would clearly be exceeded. However, the duration of intake at such high levels was considerably shorter than one year, of course.

done by different people, and the difficulty of extrapolation to other situations were cited by the committee. Nevertheless, the committee approved publication and distribution of the report primarily to "stimulate interest of the scientific community in the ^{131}I problems." There was a detailed response by Knapp.

d. Other Statements of Concern

There were many other sets of testimony at the 1963 hearings on potential overexposure of populations around NTS. Some of these were similar to the types of problems described above. Others addressed the problems in a more generic manner and included aspects of continental and global fallout.

These statements can be reviewed best by perusal of the 1963 Congressional hearings, which included testimony from committees on radiation information from various states pointing to one or more incidents of high fallout within their borders, comments by E. J. Sternglass that we will save for a separate section, a statement from Eric Reiss at Washington University in St. Louis for the Greater St. Louis Citizens Committee on Nuclear Information, and others.

Separate from the hearings was a report from LLL in 1966 that estimated thyroid doses of 50 or more rad to children in Nevada and Utah during the period 1952-1955 (Tamplin and Fisher 1966) and exceeding 100 rad for children in Washington County, Utah (St. George).

Since these reports and presentations do not involve new research information or measurements, but are primarily reinterpretations or recalculations of data already available, we recommend that the reader consult the cited hearings and the voluminous discussions of the day issued by the numerous organizations.

e. The Baneberry Event

Several years after the work of the 1960s, but still pertinent to what we are calling Phase I of the offsite exposures of people, was what is known as the "Baneberry Event." This was an underground test conducted at NTS on December 18, 1970. Unexpectedly, it vented and produced a cloud of radioactivity that ranged over central and northern Nevada and into Utah. At that time, the Biomedical Division of LLL and the Department of Radiological Health of the University of Utah were conducting cooperative studies of radioecology throughout Utah. As part of this program, designed to document the movement of already deposited radionuclides in the environment, extensive sampling operations were already in progress. The amounts in and depositions from the Baneberry cloud were thus obtained almost adventitiously. They are described with care by Pendleton et al. (1971).^(a)

There were no measurements on humans, but ample analyses were made of air filters, water, vegetation, and animal organs. The last included ^{131}I in thyroid glands of sheep, deer, and rabbits. The measurements, coupled with prediction models, were used to predict human hazard from the Baneberry venting.

(a) "The radiation doses to humans, including infants, from all significant radionuclides known or calculated to have been released in the Baneberry venting were estimated for the Salt Lake City area, where the highest air activities were observed in our sampling network. In each case, the largest potential dose was to the thyroid. The estimated dose received from inhalation and submersion was 0.005 rem to the thyroid. . . . The total dose to a child's thyroid resulting from the cow-milk pathway was calculated to be approximately 0.012 rem based upon measured concentrations of ^{131}I in hay and milk." (Pendleton et al. 1971, p. 168)

It should be noted that exceptionally heavy snowfall was on the ground, and winter feeding practices were in effect at the time of the Banberry venting. This undoubtedly prevented more significant human exposures. Calculations made for summer feeding conditions yielded a thyroid dose to children from age zero to one year of about 1.3 rem for a dry deposition condition and as high as approximately 100 rem if complete deposition of the ^{131}I in the cloud had occurred by virtue of heavy local precipitation.

f. Comment

Whether or not the details are correct or the models accurate for the cases cited, they dispel any possible lingering doubt that internal doses from fallout radionuclides bear only a tenuous relationship to the measured external gamma dose, especially on the ground. If the nuclides enter humans via the food chain, the relationship is essentially nil. This is true whether the radionuclide is strontium, cesium, or iodine. The practice of the early 1950s of relying on external gamma measurements is obviously inadequate, in retrospect.

There are strong implications in much of the testimony that the situation was not appreciated within "the establishment." Yet, there is ample indication in the literature that all parties concerned were coming to appreciate the importance of the new facts, especially about the food chain, at about the same time. (See, for example, the last part of Part 2 of the 1963 hearings.) It might be said that all were learning together as new facts were gathered.

In due course, action was taken on iodine in the form of revising the Code of Federal Regulations. The permissible level for iodine in the environment was reduced by a factor of 700 (Appendix I of Part 10, CFR 20).^(a) Also, if food is involved, restrictions on intake of any radionuclide of a factor of three may be applied (see, for example, Section 20.106e of 10 CFR 20).

There was and still is controversy as to the doses imparted to the various populations by these events. The early concentration on longer-lived nuclides like strontium and cesium has left us in better shape for reconstructing the probable doses from these than from a short-lived radionuclide like ^{131}I . The possibility that only a few members of the population received the higher doses cannot be conclusively refuted. Mays, whose work (cited above) is frequently quoted as indicating a cumulative thyroid dose from ingested ^{131}I of from 5 to 50 rad *for all children*, stated clearly in his second round of testimony (Mays 1963) that the potential 14-rad dose came from milk from one farm out of thirty-nine, and that the average dose for the farms studied was probably 1 rad. There is no question that a farm family drinking milk from their own highly contaminated source would receive high thyroid doses. However, since milk is pooled for the larger population centers and frequently shipped long distances, the average child probably received a different intake, lower than the maxima by a significant factor. On this basis, many took the view that the high doses involved only a few isolated cases (Seaborg 1963).

The dilemma must remain insofar as iodine is concerned. We can never bring back measurements that were not made, nor can we reconstruct the milk-drinking habits of these populations in the early 1950s any better than current information permits. Backward extrapolation on the basis of air concentrations

(a) Strictly speaking, this applied only to the effluents from light-water-cooled reactors. More in chapter 15.

or on the basis of yield from the devices involves assumptions piled upon assumptions and is recognized by all as subject to large errors. Yet, this is all we could or can do.^(a)

Obviously, the next step was to look for long-term biological effects in the exposed populations. We will now examine that work.

2. People—Phase II—Clinical Studies and Epidemiology

The clinical studies were a logical outgrowth of the findings detailed as "Phase I." They were considerably broader than possible thyroid pathology since there was concern also for possible increased incidence of leukemia, even of bone tumors. The work was slow to start. There were many reservations about the scientific feasibility of such studies. The population was not large by epidemiologic standards. There was also concern that mounting clinical studies would engender undue apprehension in the populations involved.^(b)

This author has in his possession a document in draft form dated July 23, 1965, entitled "Leukemia Mortality in Southwestern Utah" by Edward S. Weiss of the PHS. It is marked "Forwarded by Memo, 9-9-65," and attached to it are some formal "comments" on the plan. These comments point out the many problems in the draft report and conclude, "it is difficult to accept the idea that the observed number of cases in Iron and Washington Counties, Utah, 1950-1964, is indeed excessive, especially in the absence of information on the number of cases during the same period in equally small population groups around the country."^(c) It appears that this draft report was never published in the form written.

There was also a protocol for a clinical project to be undertaken by the National Institute of Dental Research and the National Institute of Arthritis and Metabolic Diseases for study of 2,000 residents of Washington County, Utah, and a control area. There was to be a dental study, a thyroid study, and two relatively unrelated adventitious studies. The exact fate of this plan is not clear, but it seems to have at least stimulated further work.

At the time of the 1963 Congressional hearings, both the PHS and the AEC announced plans for a study of thyroid and bone cancer, leukemia, and congenital malformations in Utah and Nevada. It was indicated that this study might serve as a pilot project to determine the feasibility of a national program. Like all studies of this nature, the results were slow in coming, partly because of the irreducible latent period for development of many of the dyscrasias under study. However, the work did get done. The results began to appear in the 1970s. We will begin with the findings concerning the thyroid.

In 1971, Weiss and colleagues from the Bureau of Radiological Health (Weiss et al. 1971) reported on the search for thyroid abnormalities, especially nodules,

- (a) The long-term persistence of ^{90}Sr and ^{137}Cs in soil, vegetation, and small mammals on NTS was confirmed as late as 1980 by Romney et al. (1981).
- (b) As it turned out, this was, like many such apprehensions, incorrect. When the work finally got under way, there was general acceptance, including enthusiasm in the groups who regarded themselves as most highly exposed. Indeed, the reaction seemed to be more along the lines of "It's about time."
- (c) It appears that the culprit was taken as the external gamma dose, and thus this work may not properly belong in this book on the effects of deposited radionuclides. However, it is part of a continuum and cannot be separated from work on radionuclides deposited in the body.

in the cogent areas of Utah and Nevada that included "exposed" and "not exposed" groups and a separate control population from Graham County in southeastern Arizona, an area that received practically no fallout from the NTS. All children of the subject communities between the ages of eleven and eighteen years attending junior or senior high school were screened by a team of three physicians in the fall of 1965. Each physician independently examined each child. In 1966-1967, the area was extended to include Lincoln County, Nevada, close to the NTS but with a small population spread over ten thousand square miles. Children with suspected abnormalities were referred to an expert review panel. This process continued to at least 1968. A total of 2,048 children from Utah and 1,440 from Arizona were studied. Of these, 71 from Utah and 25 from Arizona showed suspected thyroid abnormalities. The review panel characterized 31 (22 from Utah and 9 from Arizona) as containing single or multiple thyroid nodules. There was careful analysis of demographic features of all groups. The frequency of nodularity was equal between the "exposed" and "not exposed" groups in southwestern Utah; they were also no higher than in the control group in Arizona.

A later report that included as authors many members of the review panel from the PHS study (Rallison et al. 1974) expanded the group to 5,179 children. The conclusions were the same, viz., no significant difference in any type of thyroid disease between exposed and unexposed groups.^(a) The report was repeated with some additional work and more emphasis on thyroid nodularity as a clinical entity in 1975 (Rallison et al. 1975).^(b)

There are the usual problems of relatively small numbers in these studies from the standpoint of epidemiology. Also, it could be argued on the basis of the ten-year latent period seen in the Marshallese that the 1962 tests did not have time to express themselves. However, the incidence that seemed to peak at about age seventeen (determined by re-examination) was clearly decreasing toward the close of the study. On balance, it seems unlikely that any striking changes in thyroid structure and function could have been missed. While the data are too sparse to permit confident calculation of a risk rate (Maxon 1983),^(c) they have served their initial purpose.

These reports do not indicate whether or not the surveys turned up any other abnormalities or whether or not the dental survey was ever consummated. There was, however, a considerable effort aimed at leukemia—a recrudescence perhaps of the unpublished report of Weiss mentioned earlier. We will now turn to this.

A definitive study of leukemia, known as the "Lyon Study," was produced in the Department of Family and Community Medicine at the University of Utah (Lyon et al. 1979). The researchers divided the state into "low" and "high" fallout counties on the basis of maps of fallout patterns obtained from the Defense Nuclear Agency and the Energy Research and Development Administration (ERDA). They reviewed all deaths from childhood cancers up to age fifteen

(a) An interesting spin-off of this study was the fact that only 6 of the 201 children found to have thyroid abnormalities knew of their disease prior to examination. The authors urge careful examination of thyroids even in apparently healthy children to get more reliable base-line data for the nation as a whole.

(b) Some of these reports had earlier counterparts in "house documents" such as *Radio-logical Health Data*.

(c) The subject NCRP report has been published as Report No. 80.

years occurring in the entire state between 1944 and 1975, with a separate cohort for those under fifteen between 1951 and 1958. The authors could not distinguish between external exposures and specific isotopes entering via the food chain for the simple reason that isotopic composition was not reported before 1957. This may account for some of the perturbations of the data, since the measure of dose is, thus, quite crude.

For reasons that are quite unknown, the base-line leukemia mortality in the low-exposure cohort in the high-fallout counties was about one-half that in the remainder of the state and in the rest of the United States. Thus, any increased incidence presumed to be due to exposure to fallout in these counties is above an unusually low base line. The "high-fallout" counties were southern and eastern and are all rural in nature. The remaining "low-fallout" counties were northern and western and were more urbanized; they contained 90% of the population. The cancers were divided into two categories: leukemias and other childhood neoplasms.

The picture of leukemia incidence in the Lyon Study is given in figure 12.14A according to years of occurrence and according to exposure cohorts in figure 12.14B.

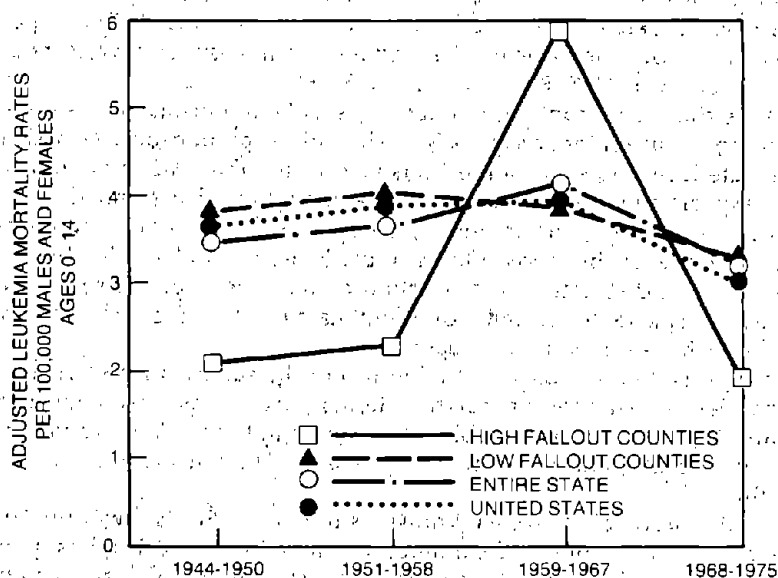


FIGURE 12.14A. Adjusted leukemia mortality rates per 100,000 population according to year of occurrence for counties with high and low fallout. (Redrawn from Lyon et al., 1979. Reprinted with permission of the *New England Journal of Medicine*, Waltham, Massachusetts, copyright 1979.)

Mortality from leukemia increased by 2.44 times in the high-exposure cohort residing in high-fallout counties and was highest in ten- to fourteen-year-old children. A gamma dose of 6 to 10 rad to the bone marrow was calculated to be needed to produce this excess of leukemia. Other childhood cancers seemed to

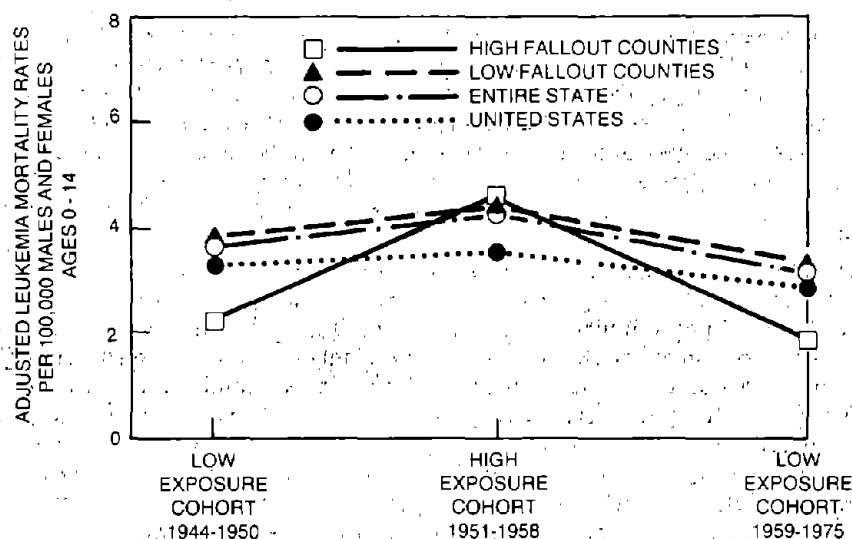


FIGURE 12.14B. Adjusted leukemia mortality rates per 100,000 population for high-exposure and low-exposure cohorts for counties with high and low fallout. (Redrawn from Lyon et al. 1979. Reprinted with permission of the *New England Journal of Medicine*, Waltham, Massachusetts, copyright 1979.)

decrease during this period. Despite the apparent circumstantial evidence, the authors state "the increase in leukemia deaths could be due to fallout or to some other unexplained factor" (Lyon et al. 1979, p. 397).

As with most epidemiologic studies involving rather small and shifting populations (the high-fallout areas have been losing population steadily since the 1940s, especially in the younger age groups), there are problems with drawing any conclusions. Land, at the National Cancer Institute (Land 1979), takes the position that the control group should be greatly expanded. He is also troubled by the possible interpretation of the data (which he demonstrates) that fallout produced *both* an increase in leukemia mortality and a decrease in other childhood cancers during those years. It is indeed notable that the primary effect in the cohort study was to bring the rate up to that in the low-fallout counties and slightly above that in the rest of the United States. Does this have anything to do with fallout or radiation, or is it quite a different phenomenon? Land reserves judgment as to causation versus artifactual explanations.

James Enstrom, a cancer epidemiologist at UCLA and program director for cancer control epidemiology at the UCLA Comprehensive Cancer Center, was sufficiently concerned over the possible unwarranted extrapolation of the Lyon Study in the public mind that he wrote a detailed article for the *Los Angeles Times* (Enstrom 1979). He expanded upon it in the report on the Baneberry incident (Enstrom 1980). He states, "Once all of the available statistical evidence is considered and these findings put into perspective, however, no reasonable person could conclude that nuclear fall-out from Nevada has caused any excess leukemia mortality." He considers that at no time during the total period of analysis (1944 through 1975) was the leukemia rate in the high-fallout counties

truly different from rates of Utah or the rest of the United States. Also, leukemia in southern Utah comprised only about 1% of the reported deaths under fifteen years of age, while they comprise about 2% in an average Utah population. He raises other questions, e.g., Were the diagnoses reliable? (The number of board-certified specialists in the high-fallout counties is considerably lower than in the more urbanized areas.)^(a) Radiation doses were never measured in the individuals succumbing to leukemia to see if they were higher than in those that did not.

Klauber (1980) discussed other problems with the study, including migration, time trends, statistical significance, etc. He does not disown the tentative conclusions but joined others in recommending caution, particularly because of the tendency for cancer mortality rates to vary widely with time in small populations.

Since these studies were, at best, equivocal for leukemia and clearly negative for thyroid changes, there was agitation to mount a much larger, more comprehensive study. The Bureau of Radiological Health of the PHS undertook a feasibility study for such a broader investigation, one including the entire populations of Utah, Nevada, and Arizona (Hoffman, Harlow, and Tully 1981). They addressed, among other problems, the knotty question of locating and resurveying the previously studied groups. The report gives an excellent review of the work done from 1964 on under their auspices. The test cases put into the study indicated that it would be feasible to conduct a full-scale follow-up, but only if the strengths and weaknesses of various options were fully appreciated.

So far as this author can find, personnel and funds that might have been thrown into such a follow-up study have had to be diverted to the events we will describe under the heading "People—Phase III." However, investigators at the National Cancer Institute did follow up using cancer mortality data from the National Center for Health Statistics and published a complete review of the enterprise (Land, McKay, and Machado 1984). This very recent re-examination concludes that there is "no pattern of temporal and geographic variation in risk supportive of the reported association [between childhood leukemia and radioactive fallout]." It is suggested that "the purported association merely reflects an anomalously low leukemia rate in Southern Utah during the period 1944 to 1949." This addition is not a substitute for the very broad investigation envisaged in the feasibility study, but it appears to represent the most that can be concluded from the data at hand.

3. People—Phase III—Litigation

It was probably inevitable that contention, bitterness, and litigation should come to the events and the people we have been describing. It was a logical extension of public apprehension regarding nuclear energy and nuclear weapons. Details do not belong in a book devoted to scientific research on the health effects of radioactive materials. Also, obviously we cannot say anything about items still under litigation. However, some samples of the activities are pertinent.

First, let us put to rest the mistaken notion that there were no proper standards for fallout at the time of the tests most involved in the litigation. Section VII devotes considerable space to standards for fallout and describes in detail the recommendations in place under AEC auspices in 1953. The problems were

(a) This could, of course, work both ways if there were many cases missed during the periods of high fallout.

not primarily those of knowing how much was too much but of predicting where the fallout would go and in what quantities, as well as deploying personnel and measuring devices in the right place at the right time. Collection of global fallout was easier. Establishing the real behavior of clouds wandering over hundreds to thousands of square miles of terrain was a new and very challenging task.

Second, the onset of litigation stimulated much new research, both archival and experimental.

One thing is quite certain. The role of radionuclides in the possible production of radiation doses and possible health effects was now receiving emphasis whether it played an important role or not (see discussion of "the hidden dose" in section VIII).

The agitation seems to have been sparked by some lawyers, notably Stewart Udall of Arizona. The time was ripe. Cancer incidence in the populations exposed in the 1951-1962 era was bound to increase since this group was now entering the age range when cancer incidence normally peaks. It is not surprising that many of the exposed individuals began to wonder if their cancer or that of family members had been caused by the increased radiation levels during the tests. There was also a residuum of resentment at events of the earlier years variously depicted as "being exposed without consent or knowledge," "withholding of information," on up to culpable negligence on the part of the U.S. government.

The process was brought into focus by the Radiation Exposure Compensation Act of 1981 (#S 1483) introduced in the U.S. Senate under the sponsorship of Senator Orin Hatch of Utah. The act came before the Senate Committee on Labor and Human Resources; it was revised and reviewed in 1982. Its primary objective was to "construct a proper remedy" so that those whose cancer was clearly related to fallout would be compensated by a just and compassionate government. The most thorny question has been and continues to be the establishment of criteria for "clearly related to fallout." Since there is no way to distinguish between a cancer produced by radiation and a "natural" cancer, a new approach called the *probability of causation* was added to the conventional ones already being used. This approach was formulated by Victor Bond at BNL and championed by the NCRP (Bond 1981a,b, 1982). The formulation calculates the odds that radiation was causative as follows:

$$\frac{R_R}{R_N + R_R + R_O + R_A}$$

where R_R is the risk of cancer from a given dose of fallout radiation in a specific situation; R_N is the natural risk of the particular type of cancer; R_O is the risk from other radiation exposures, such as medical diagnosis and treatment; and R_A is the risk of that cancer from other carcinogenic agents or processes, either environmental or occupational. Theoretically, all that is needed is a decision as to the level of odds (i.e., the ratio) above which compensation should be guaranteed. In practice, the quantitation of risks in the variety of situations encountered in these cases is far from easy.^(a) Nevertheless, the idea is interesting

(a) It could be imagined also that if part of the radiation dose was external and part from internally deposited radionuclides, and if the risks were different, two factors for R_R might be needed. However, Bond and most others using the formulation consider the main risk to be from the external dose and neglect the internal dose.

since, otherwise, compensation might get completely out of hand and radiation become nominally responsible for almost any cancer in any individual who could prove exposure. The costs could be in the billions of dollars.

With potential costs of such magnitude and an atmosphere of bitterness and acrimony developing, the U.S. government through its Department of Energy organized the Coordination and Information Center in Las Vegas described in chapter 11. The Offsite Radiation Exposure Review Project under the Nevada Operations Office of the DOE was also organized. The project and deputy project managers are R. W. Newman and M. Page, Jr., respectively. There was close coordination with the National Laboratories (particularly LLL), the firms involved in the engineering aspects of the tests (e.g., REECO, and Holmes and Narver), and also with other government agencies (e.g., DoD and EPA). The purpose was a complete review and recapitulation of all pertinent data and, if possible, reinterpretation of doses in the light of new knowledge.

A central place in the process has been occupied by the Dose Assessment Advisory Group (DAAG) with Bruce Church as project officer. This sixteen-member advisory group, chaired until recently by Robert Moseley, a radiologist from the University of New Mexico, is broadly based with physicists, radiobiologists, toxicologists, health physicists, epidemiologists, people from the Disease Control Centers, a lawyer,^(a) and a medical school dean. They are receiving almost as much testimony as the Joint Committee on Atomic Energy of the Congress received in the 1950s and 1960s. Lawrence Livermore National Laboratory has been especially active in supplying data and penetrating analyses for both external and internal dose.

We will consider some recent testimony to the DAAG presently. However, several other events should be discussed first since they took place earlier; all are related and bear on the same basic problems.

As part of the review process, an important capsule summary of research on internal emitters stimulated by and bearing on the problems of fallout was prepared by Book and Goldman (1983) at the Laboratory of Energy Related Health Research at the University of California at Davis. This does not attempt to introduce new material but is a cogent and succinct summary.^(b)

During 1979-1980, Bernard Shleien, at the Bureau of Radiological Health, Food and Drug Administration, reviewed all possible measurements of external radiation to the approximately 188,000 persons around NTS exposed to test-generated fallout (Shleien 1981b). The highest cumulative exposure at a populated site was 17.5 R, with fourteen persons receiving over 17 R, calculated as exposure to infinity. The cumulative infinity exposures and number of persons in each dose range as computed by Shleien are shown in table 12.12. Obviously, a majority of persons in this tabulation, estimated by Shleien as about 157,000, received external gamma doses below 0.5 R per annum, the accepted maximum permissible dose for individual members of the public.

(a) It is not clear to this author how a lawyer can help technically with radiation dose assessment, but perhaps he can advise on the evidentiary value of different types of information.

(b) As indicated at the beginning of this chapter, this compendium has been used at many junctures in this chapter, particularly for reference reminders, and the author is most grateful to Dr. Goldman for supplying a copy.

TABLE 12.12. Offsite NTS Cumulative Infinity Exposure (in R)

Cumulative Infinity ^{***} Exposure (R)	Number of Persons in Exposed Group
>17.0	14*
9.0-16.99	17**
8.0-8.99	769
7.0-7.99	10
6.0-6.99	6,563
5.0-5.99	165
4.0-4.99	114
3.0-3.99	2,999
2.0-2.99	766
1.0-1.99	17,889
0.5-0.99	2,420
<0.5	156,756

*Varied from 2-14 persons.

**As noted in the text, previously published reports (TMC 1959) give higher external gamma measurements (or estimates) than corroborated in this study for several locations. These earlier reports would indicate that between 5 and 550 persons resided at populated sites that could have experienced a cumulative infinity exposure of greater than 10 R.

Source: Modified from Shleien 1981b. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1981.

Collective exposure commitments in this population ran from 1,700 Person-R for Lincoln Mine with a population of 200, to 35,000 Person-R for St. George with a population of 5,000. Las Vegas showed 16,900 Person-R for a population of 60,000 or about 0.28 R per person.

A far-ranging review of external radiation dose estimates offsite and a summary of the environmental monitoring procedures and results were presented by Wrenn at the sixteenth annual meeting of the NCRP in April 1980 (Wrenn 1981a). He also summarized the new research stimulated by the problems of litigation and the needs for future studies. His conclusions are in the same range as those just reviewed. They include dose rate as well as "infinity doses" and quote conclusions of the Interagency Task Force on Compensation for Radiation Related Illness (Phase I report) that "among the 172,000 residents downwind [of NTS] there might eventually be expected to occur 18 to 40 cancers of which 6 to 16 should be fatal." This estimate utilized risk estimates from the 1980 BEIR report.

A possibly important gap in these reanalyses is the lack of determination of any possible contributions from ingestion or inhalation. As we have already seen, these may be negligible for a majority of radionuclides but cannot be ignored, for iodine, for example. An unexplained anomaly, noted in the table 12.12 footnote, is the difference between the computed external gamma measurements published in 1959 by the Test Managers' Committee to establish fallout doses (Shelton et al. 1959) and those in more recent reports. At several locations, the new work showed lower doses. The communities involved were small, and the effect of the difference on cumulative overall doses is small. No explanation is apparent. It may lie in matters of interpolation between communities in which no actual measurements were made (Ansbaugh 1979).

An important further addition to the dosimetry, again the external dose, was based not on reanalysis of the old maps and records but on measurements of residual ^{137}Cs and plutonium in soil (Beck and Krey 1983). This was a project of the Environmental Measurements Laboratory (EML), formerly Health and Safety Laboratory (HASL), in New York. They took soil samples from over 150 sites, mostly grass-covered lawns in towns or on farms that were "verified through local sources to have been undisturbed for at least 30 years except for watering and minor maintenance." It was reasoned that these would give as clear a picture as possible of the total deposition and stratification of fallout radionuclides with time. From eight to ten core samples were taken at each of the 150 sites. Analyses were made of the 662-keV gamma-ray from ^{137}Cs at several depths up to 30 cm, and radiochemical analyses were performed for ^{239}Pu plus ^{240}Pu , and for the mass isotopic composition. Many additional sites were surveyed by in-situ gamma spectrometry without the hassle of getting a good soil sample.

Global fallout had contributed significantly more of these isotopes than the local NTS fallout. Therefore, it was necessary to ascertain what portion of each sample activity represented NTS fallout. This was made possible by the difference in the $^{240}\text{Pu}/^{239}\text{Pu}$ ratio between NTS and global fallout. It was much higher for global fallout from the high-yield Pacific tests.

A comparison of the integral exposure estimated by the soil core method to that from monitoring data is given in table 12.13A. Note the very reasonable agreement between the two disparate methods. Estimations of exposures to both individuals (population weighted) and populations obtained by this method are shown in table 12.13B.

TABLE 12.13A. Comparison of Integral Exposure Estimates with Estimates [from soil cores] Based on Monitoring Data Obtained after the Tests at NTS. Values in parentheses are percent uncertainties. The estimated uncertainties in the monitoring data range from ± 40 to 60 percent.

Town	Exposure Estimate (R)	
	This Article	Monitoring Data
Beaver	≤ 0.6	0.5
Cedar City	0.6 (100)	0.9
Enterprise	1.7 (30)	1.3
Hatch	≤ 0.6	1.1
Hurricane-La Verkin	4.2 (50)	6.5
Kanab	0.7 (100)	2.9
Kanarraville	0.7 (300)	2.9
Milford	≤ 0.6	0.2
Minersville	0.6 (200)	0.4
Modena	≤ 0.6	1.0
Mt. Carmel	≤ 0.6	1.6
Panquitch	0.4 (100)	0.8
Parowan	1.1 (80)	0.8
St. George	3.7 (25)	6.1
Veyo	5.9 (100)	4.5
Washington	2.4 (100)	5.8

Source: Reset from Beck and Krey 1983. Reprinted with permission of Science, Washington, D.C., copyright 1983.

TABLE 12.13B. Estimates of Population Exposure by County

County	1950 Population (x 10 ³)	Population-Weighted Mean Individual Exposure (R)	Population Exposure (x 10 ³ Person-R)
<i>"Low-Fallout" Counties*</i>			
Box Elder	19.7	0.6 ± 0.6	10
Tooele	14.6	0.7 ± 0.7	10
Cache	33.5	1.1 ± 0.7	37
Rich	1.7	~1.1 ± 1.1†	1.9
Weber	83.3	1.8 ± 0.5	150
Davis	30.9	1.3 ± 0.5	40
Morgan	2.5	~1.5 ± 0.8	3.8
Salt Lake	275.0	1.2 ± 0.5	330
Summit	6.7	1.1 ± 0.7	7.4
Daggett	0.4	~0.7 ± 0.7	0.3
Wasatch	5.6	0.5 ± 0.5	3
Utah	81.9	1.5 ± 0.5	120
All counties	556	1.3 ± 0.3	713
<i>"High-Fallout" Counties*</i>			
Juab	6.0	0.6 ± 0.4	4
Millard	9.4	1.5 ± 0.4	14
Beaver	4.9	0.7 ± 0.5	3
Iron	9.6	0.7 ± 0.5	7
Washington	9.8	3.5 ± 0.7	34
Kane	2.3	0.7 ± 0.7	2
Garfield	4.2	0.4 ± 0.4	2
Piute	1.9	~0.8 ± 0.8	1
Wayne	2.2	~0.8 ± 0.8	2
Sevier	12.1	0.2 ± 0.4	2
Sanpete	13.9	0.5 ± 0.4	7
Emery	6.3	1.9 ± 1.1	12
Carbon	24.9	0.3 ± 0.2	8
Duchesne	8.1	0.2 ± 0.3	2
Uintah	10.3	0.7 ± 0.5	7
Grand	1.9	0.9 ± 0.9	2
San Juan	5.3	1.1 ± 1.2	6
All counties	133	0.86 ± 0.14	115
State total	689	1.2 ± 0.2	828

* As defined by Lyon et al.

† The symbol ~ indicates that the value was extrapolated from neighboring counties.

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The EML work addresses the fact that average bone doses in Washington County were ten times those from global fallout in the United States, while they were four times greater than for external exposure to fallout in the northern Utah counties.

Beck and Krey conclude that the doses calculated for all areas are below those required to produce a significant mortality excess from leukemia (using

2×10^{-5} per rad as the average lifetime risk for radiogenic leukemia). This is based, of course, on the external gamma dose alone.

At least three other new approaches are seen in the proposals made by McDonald E. Wrenn, University of Utah, as part of his testimony on U.S. Senate Bill #S1483^(a) on October 27, 1981 (Wrenn 1981a). The first approach utilizes measurements of the radioactivity of quartz grains in bricks from houses in the areas of interest. The quartz in the bricks is made slightly more radioactive than in its natural state by the extra gamma flux in the environment from passing and deposited fallout. This is cumulative from the time the brick was removed from the kiln in which it was fired and can be measured by the strength of the stored thermoluminescent signal. Since background radioactivity in these bricks is more or less constant, any excess found in a given location can be considered due to radiation from fallout. Fortunately, the method is quite sensitive and not many bricks are needed from any one location!^(b) Results of this work are not yet available.

A second approach proposed by Wrenn and his colleagues may give a better way to reconstruct the amounts of iodine isotopes in fallout from the different events. Of the several iodine isotopes in fallout, one, ^{129}I , has a half-life of sixteen million years and will, thus, be present indefinitely in any sample in which it can be measured. Fortunately, it is formed in fixed proportion to ^{131}I and can thus indicate amounts of the latter originally present.

The Utah investigators' plan is to use an ultrasensitive technique and measure ^{129}I in the tissue blocks (small samples routinely taken for pathology work) of thyroid tissues stored at the Salt Lake City VA Hospital.^(c) Results are not available yet from these studies either, but if a sufficient geographic spread of samples is available, they should be of considerable interest.

Finally, Wrenn (1981b) proposed to measure the residual plutonium in human tissues similarly stored. The proposal is to select cases that could only have received the plutonium by inhalation of fallout. This will take some doing, and the numbers may be rather small.

We come now to the type of data presented to the DAAG.^(d) Many of the calculations are tied to specific litigants and, therefore, cannot be quoted here. However, much is not enmeshed with the litigations and can be summarized as follows:

1. An in-depth review of the fallout contour maps, the way they were constructed, and some selective rechecks indicated that many of the old contour lines needed modification. This was particularly true of many of the areas designated as "hot spots." Many of these were found in fact not to exist now or ever to have existed, although other hot spots were fully confirmed. These new interpretations were incorporated into revised dose estimates.

(a) The Radiation Exposure Compensation Act.

(b) This is, of course, reminiscent of methodology used by archeologists to measure the age of fired pottery (Wrenn 1981a).

(c) Fortunately, most hospitals keep their pathology tissue blocks available for many years for possible rechecks.

(d) This author is indebted to Marshall Page, Jr., deputy project manager of the Offsite Radiation Exposure Review Project, for copies of typical transcripts of these meetings.

2. Details of the technique used for each community are presented including not just surface fallout but events at various altitudes; numerous maps are presented.
3. There was a thorough review of the lifestyle, agricultural practices, housing, and all similar factors that might bear on dose to the inhabitants through the food chain.
4. Much soil-sample work was done on both old and recently collected samples. This ranged over the country far from the areas of high local fallout.
5. Assessment was made of the dose from internal emitters and external dose to skin, whole body, red bone marrow, lower large intestine, thyroid, kidney, liver, lung, and testis. Also, the probable dose to a fetus in utero was constructed. This was done individually for each litigant and each event, an enormous task done largely by the biology group at LLL. Other tissues were added for certain cases.
6. It was determined which radionuclides contributed certain percentages or more of the dose to selected organs, and the cumulative dose from each was calculated and summed with the others.
7. The nuclides that contribute 1% or more to the thyroid dose were ^{131}I , ^{132}Te , and ^{133}I .
8. The radionuclides contributing 5% or more of the dose to the lower large intestine were ^{239}Np , ^{89}Sr , ^{93}Y , ^{97}Zr , ^{140}Ba , and ^{147}Nd .
9. The radionuclides contributing most to bone marrow dose were ^{89}Sr , ^{90}Sr , ^{131}I , ^{132}Te , ^{137}Cs , and ^{140}Ba . (a)

The analysis sums the dose over all nuclides and all events to which the given litigant had probably been exposed. There was even comparison of different schemes for calculating internal dose, e.g., LLNL, MIRD, ICRP-30, etc. (see chapter 16). Some of the calculated thyroid doses were in the range of 30 to 40 rad. Most of the other internal dose contributions were considerably smaller. Any further details will have to await completion of the work and the end of the litigations, if this ever comes about. (b)

We cannot help but be impressed by the amount of information that could be and has been brought to bear on these specific cases. Whether it will prove

(a) The listings in items 7, 8, and 9 above came from a presentation by Drs. L. R. Anspaugh and Yook Ng, Lawrence Livermore National Laboratory (LLNL) at the January 7, 1983, meeting of the DAAG.

(b) L. R. Anspaugh from LLL and Bruce W. Church from DOE, Nevada Operations Office, have just published historical estimates of external gamma exposures from operations at NTS through Test Hardtack II, 1958 (*Health Physics* 51: 35-51, July 1986). These give a total collective external gamma exposure of 85,000 person-R, with three localities receiving major portions of this (note *collective*, not individual dose, which is much smaller) viz., St. George, Utah; Ely, Nevada; and Las Vegas, Nevada. The figures update those given herein. Also, the authors indicate that this is a part of a seven-year project to determine radiation doses received by residents in the region of NTS. They also stress that the data do not include any consideration of inhalation or ingestion of radionuclides. This must await completion of a major project under way to reconstruct and report "all significant pathways of exposure and dose." Thus, we will still have to wait a while for answers to some of the major questions raised in this chapter.

sufficient to render an unequivocal, or at least a satisfactory judgment of the probability of harm, only the future can tell. (a,b)

- (a) It should be noted that on January 4, 1983, President Reagan signed a bill directing the government to "study the issue more carefully" (Smith 1983). The Department of Health and Human Services was ordered "to develop better estimates of the radiation doses to human thyroids from the fallout, and to relate the doses to a probable incidence of cancer..." (Smith 1983). Further, the department was ordered to prepare statistical tables that indicate the likelihood of contracting cancer after exposure to specific doses of ionizing radiation over the range 1 millirad to 1,000 rad. It was also required that the data be presented in a manner that would allow determination of the probability of causation.

The idea is obviously to prepare a model for determining how much compensation each exposed individual should get—a laudable objective.

The first provision is simply an extension of the work already under way and described in the section above. In view of the enormous effort already expended, it is hard to see how really new information can be found unless some of the more novel approaches described in this chapter bring in unexpected results. The order to cover the range from 1 millirad to more than 1,000 rad is asking for the solution by fiat of the problem of dose-effect relationships that the biomedical community has been struggling with for decades. (This may be why President Reagan is said to have signed the bill "reluctantly.") Such statistical tables all in one place will undoubtedly be useful, but the low-dose range will have to be done by extrapolation, just as it is now. If the lawmakers really want a better solution to the low-dose problem, generous support of thorough research into basic biological phenomena might hold greater promise in the long run.

- (b) On May 9, 1984, Judge Bruce Jenkins in Salt Lake City ruled that ten cases of cancer in the exposed civilian population in Utah had been caused by the radiation from fallout radionuclides from the NTS and that the U.S. government had "unreasonably placed plaintiffs or their predecessors at risk of injury" (Smith 1984). The conclusion involved seven cases of leukemia and one each of breast cancer, thyroid cancer, and lymphoma. Obviously, the ruling can be expected to apply to dozens of similar claims and have "enormous legal and economic repercussions" (Smith 1984).

The ruling criticizes especially the lack of monitoring of radiation exposures of vulnerable individuals, particularly children, by the use of film badges, counting of thyroids, or whole-body or blood counts. It also cites the potential for "hot spots," discussed repeatedly in the reports and in the preceding pages of this chapter, for creating radiation doses considerably higher than those stated publicly as having occurred. It also states that more was known about the amount of strontium deposited in the bones of the people of Nepal, Norway, or Austria than of the residents of St. George, Cedar City, or Fredonia, which lay directly in the path of fallout.

It may be that all that is left now is determination of the size of the compensation for the many other potential cases. Yet, the scientific work continues, as do differences of opinion as to what the scientific as opposed to legal conclusions should be. This is still for the future to tell. In any event, the whole episode has stimulated scientific detective work that will be useful in many other connections and has advanced significantly our knowledge of the knotty problems of the long-term effects of low-level radiation exposures. Only a full explanation of the mechanism of radiation-induced cancer and the doses necessary can resolve the scientific question. Yet, the enormous scientific efforts stimulated by the problems of fallout and detailed in this and following chapters have great value irrespective of any legal decisions on blame for injury or its causation.

4. Sheep

A controversy of proportions almost comparable to that described above for human populations around NTS arose in connection with farm and range animals. It did very little to further our understanding of the health effects of radionuclides but was of consuming importance to those concerned. We will review it briefly with emphasis on the scientific aspects.

We saw in the discussion of the first shot, Trinity, that cattle could receive beta burns from deposition of fallout radionuclides on their backs. However, as we will see in chapter 13, these did relatively little damage to the overall health of the animals. In the earlier days of operation of NTS, offsite ranchers made claims (and received settlements) for injury to their cattle from fallout (e.g., U.S. Congress 1955). It was customary to keep a wary eye out for wandering cattle near the test site when shots were planned, but, as the dimensions grew, so did the difficulty of such surveys.

The incident (or incidents) of concern here involved the unexplained deaths of hundreds of sheep and lambs, particularly at lambing time, in and near ranching communities of southeast Utah (e.g., Cedar City). This occurred in the spring and summer of 1953. Fallout from two tests in the Upshot-Knothole series (Shot "Nancy," 24.4 kt fired on March 24, 1953; and Shot "Harry," 32.4 kt fired on May 19, 1953) were accused of being responsible for the sheep and lamb deaths. The exposures may have occurred partly during the "trail back" process from Nevada to Utah, partly at the site of lambing.

The AEC and the state of Utah sent in veterinarians to examine the animals. They were joined by representatives of the Bureau of Animal Industry of the U.S. Department of Agriculture, the PHS, and the U.S. Army Veterinary Corps. Some of these individuals had had in-depth experience in radiation pathology; others had none. A large number of the sheep deaths had already occurred by the time this cadre of experts was convened. Hence, firsthand observation by the experts was rare.

The lesions that were observed did not in general resemble the classic lesions associated with radiation exposure. They should have, because many of the deaths occurred within relatively short periods after the exposure, and exposures massive enough to be fatal in a short period would be expected to show definite effects in a majority of the animals. Examination of animals dying shortly afterward and said by the owners to resemble those that died earlier, gave no evidence of classic radiation damage. The absence of damage was confirmed pathologically by an examination of the tissues of animals that were selected by the owners as representative of their damaged flocks (Bustad et al. 1953).

From this point on, the story becomes more and more confused and complex. It had been a dry cold winter, and the animals were in poor physical condition. It was also considered possible that the animals had drunk "bad water" en route from winter range. They were undernourished. There was a severe snowstorm at lambing time. Could these circumstances have made the animals unusually sensitive to radiation? To check this out, investigators at Hanford undertook a special experiment as a supplement to the large laboratory/field experiment described in chapter 8. They mounted "The Triple Radiation Assault" experiment (George, Hackett, and Bustad 1957). Sheep from the laboratory herd were subjected to a combination of starvation, application of plaques of beta-emitting radionuclides to cause beta burns, oral administration of ^{131}I , and whole-body gamma irradiation. While there was no doubt that this combination

added insult to injury, the type of synergism of effects required to explain the sheep deaths was not evident.

The issue, as a public and legal concern, subsided for a number of years but was resurrected in the late 1970s. Gastrointestinal-tract damage from ingestion of fission products was proposed as the central cause (Knapp 1979), despite the fact that this development would have been accompanied by massive bouts of diarrhea, both on the trail and at Cedar City.^(a) It was not. There were problems with reconstructing the dose (Koranda, Anspaugh, and Ng 1982). The media began a constant drum beat (Holden, 1980; Smith 1982 a, b).

Litigation by the ranchers against the U.S. government in 1956 had resulted in a verdict in favor of the government. In 1982, the case was reopened against the government as well as against some individual scientists, who had served as government witnesses in the previous trial, on grounds of withholding evidence, concealing data, etc. A verdict was rendered in favor of the plaintiffs by the judge who had heard the case in 1956. However, his verdict was overturned by a three-judge panel of the Tenth U.S. Court of Appeals. The plaintiffs then appealed to the entire Court of Appeals, but the entire panel affirmed the decision of the three judges. Upon further appeal, in January 1986, the U.S. Supreme Court denied further review of the matter, thus upholding the decision of the Court of Appeals. The U.S. District Court in Salt Lake City dismissed the plaintiff's action against the individual scientists "with prejudice on the merits" in March 1986.

Unfortunately, and despite much digging, little new scientific information was uncovered in these many-layered proceedings. Any further discussion of this matter is considered inappropriate to a book devoted to scientific research.

E. Onsite Exposures

1. Workers

Onsite exposure problems with workers in the various civilian organizations at NTS appear to have been relatively well controlled. The limits for worker exposure onsite were set in the very first series, Buster-Jangle, at approximately the level used in AEC contractor plants. Ordinarily this limit was 3 R (gamma radiation only) for the whole series with 3.9 R allowed in special cases (see section on Standards for Fallout).^(b) This compared well to the then-current plant limits of 0.3 R per week. Much the same operational limit was applied for Upshot-Knothole in the next year. It was 3 R based on the three-month operational period. This carried on to subsequent test series with a few exceptions.

The development and acceptance of these limits by the various components of the test organizations is traced series-by-series and shot-by-shot in the book by Hacker on radiological safety in the nuclear weapons testing program. The limits were designated for external radiation dose from the prompt radiation and the fallout cloud. They were measured by film badges or gamma survey instruments.^(c) *The philosophy that internal dose would automatically be taken*

(a) That is, the gastrointestinal-tract syndrome in acute radiation damage.

(b) No further exposure was permitted individuals who reached this limit.

(c) Recently, the government has sent many individual workers copies of their file of such exposure records.

care of by not exceeding the external limits held full sway. There were occasional bioassays, nose swipes, etc., to check for internal emitter contamination of personnel. In general, the figures resulting from these checks were low enough to validate the basic philosophy. If work was to be done in a known contaminated area, full protective clothing was worn, including respirators. The rules were strict and fairly rigidly enforced. Bioassay procedures were, it seems, regular in these instances,^(a) but this author is not in a position to judge their adequacy.

Thus, records pertinent to possible internal emitter contamination are sparse except for operations with known potential for same (see chapter 14).^(b) Potential problems in this hiatus can be seen. For example, in a review of much of the literature bearing on exposures to low levels of radiation (Marx 1979), the ideas of Alice Stewart are noted, viz., that inhaled or ingested radioactive dust from atomic-bomb blasts produced the leukemias seen in the Japanese, while the solid tumors resulted from the external radiation. This untested hypothesis is more an example of the type of thinking that may have to be dealt with in future reviews of worker health at NTS than of actualities. In general, as we have seen throughout this book, the induction of leukemia by deposited radionuclides is of less significance at low doses than other effects. It is, in general, more likely to result from whole-body external gamma doses.

It cannot be concluded with certainty that internal emitter contamination from earlier deposited radioactivity played no role in later shots at NTS. Workers did enter areas that had contamination residual from earlier operations. However, radioactive decay played an important role in reducing such contamination in terms of short-term or acute effects. It is only around long-term effects from low levels that some questions might be raised.

On the whole, overexposures of NTS workers to radionuclides at NTS do not seem to have been a serious problem.^(c) Hacker's book will give much more detail, including the exceptions.

2. Atomic Veterans

The situation for the atomic veterans is rather different. It involves the military personnel who participated in the many troop exercises and maneuvers in connection with several of the Nevada tests. There were over 250,000 participants from the DoD in the atmospheric nuclear tests carried out between 1945 and 1962 in Nevada and in the Pacific. Many of these were in Nevada for exercises termed "Desert Rock I, II . . ." etc. These exercises involved a much more intimate relation to the devices than in the Pacific since the yields were smaller and the military wished to have troops gain firsthand experience with possible nuclear artillery, etc. They are described in considerable detail by Hacker. Sometimes there was more than one Desert Rock exercise in an NTS series. The number of participants was fairly large, and the shots were not always small. Desert Rock V, for example, (associated with the Upshot-Knothole series) involved over thirteen thousand troops in mock battles and another two

(a) Such information is collected in the Las Vegas library described earlier.

(b) Exposure records from film badges, etc., are reasonably complete.

(c) Many of the old-time test personnel have made it a point to get whole-body counts at intervals. Andrews (1985) reports that his own counts indicated essentially no detectable retention of radionuclides associated with the tests.

thousand to run the camp. The radiation safety standards for the earlier Desert Rock events were pegged at the same level as for AEC contractor workers. However, the military wanted their troops to have closer encounters with atomic weapons and requested higher levels, e.g., 6 R for an exercise (Hacker undated). This was not accepted easily by AEC, but finally it was agreed that the military could operate with somewhat higher doses if they let everyone know that the DoD was taking the responsibility.^(a)

There was a problem that, beginning with the Upshot-Knothole series, sampling of the clouds of fallout and debris was done by manned planes rather than by drones. The military sought to allow aviators selected for this duty to receive exposures of 20 R or even higher so long as there was no new exposure for two years (Hacker undated). Also, there were circumstances where volunteers were stationed much closer to ground zero than a 3-R limit would permit.

Again, these dose limits were for external gamma radiation. The chances of inhalation or ingestion were obviously greater in some of these operations than for civilian workers. Troops describe being surrounded by clouds of dust in their trenches. While it is assumed that the cloud-sampling aviators wore full protective clothing and respirators, the chances of leakage, carelessness, or excess zeal to collect the precious cloud samples cannot be denied.

In 1977, the PHS Centers for Disease Control in Atlanta discovered a "cluster" of possible cases of leukemia among military participants in an especially dirty shot in the Plumbbob series in 1957, viz., Shot "Smoky." Without hesitation, DoD began a wide-range program to identify participants in the various exercises. The documentation was undertaken by the Defense Nuclear Agency (DNA), and the program was termed "Nuclear Test Personnel Review."

The word was spread through various media for participants in any of the atmospheric nuclear tests to contact the DNA. Also, servicemen who could establish participation in the exercises and had health problems were advised to contact the nearest Veterans Administration Hospital for a free physical examination. If they had leukemia or other forms of malignancy, they were essentially guaranteed care at a government facility.

Unfortunately, large gaps have occurred in the records of many servicemen due to a disastrous fire in a storage facility in St. Louis some years ago. Thus, the objective of a neat reconstruction of exactly where all individuals were, their probable doses, and thus the probability of causation of their cancer (see section V D), has not been realized in full. It may well be that there will be blanket payments based on very broad criteria.

We again have the dilemma of the contribution of internal emitters. Obviously, there was more reason to anticipate a role of radionuclides in the military than in the civilian worker exposures.

Relatively little new research has been mounted to address this question. Most of the evidence comes from retrospection. A project by the Advanced Research and Applications Corporation (Lee et al. 1983) has calculated committed organ doses received by selected military test personnel. The only doses of significance came from the notorious Bravo test in the Pacific (see section III D). There have been other such analyses using the same techniques as we described for the Utah-Nevada civilian residents. The continuity of records is, of course, a

(a) This nuance has frequently been forgotten.

much greater problem than for the relatively stable populations of rural Utah and Nevada. In 1985, a National Research Council Report (Smith 1985) concluded that there was "no consistent or statistically significant evidence for an increase in leukemia or other malignant disease in nuclear test participants." This report has, of course, been challenged, and the pot still boils.

Only a few measurements for body burden of radionuclides in the exposed military personnel have been made and formally reported. Toohey et al. (1981) used the ANL counting facilities to measure whole-body and thorax gamma-ray emissions and used urinalyses for ^{239}Pu . They measured sixteen former military personnel who were present at Shot Smoky, but could find no evidence of radioactivity above that found in the general population. Probably other such measurements should be made. Also, personnel who had counts done informally should be surveyed formally.

Very recently, it was announced that the British Ministry of Defense had announced a plan to survey twelve thousand servicemen and civilians involved in their nuclear weapons testing in the South Pacific. Evidently there had been claims of abnormally high risks of cancer in this population too (Dickson 1983). They will need to go through the same travail as we have in the United States, including some measures of the possible long-term role of radionuclide ingestion or inhalation.

VI. Nationwide and Worldwide Fallout

A. Introduction

Enough has been said already in this chapter to make it obvious that the summation of the hundreds of tests would produce contamination of the total atmosphere, of the lithosphere, the hydrosphere, and of the biosphere on a global scale. This led to by far the greatest volume of measurements, discussion, argumentation, and concern of any of the aspects of the fallout problem. It also led to much bona fide research regarding phenomena in fallout fields and the biokinetics of fallout radionuclides in man, animals, and the diet. It led to thousands of measurements, whose ultimate objective was to determine concentrations of radionuclides from which amounts in the biosphere could be predicted and other thousands of measurements on suitable samples of biological material from which dose calculations could be made.

The chances of seeing biological effects in the field at the low levels of radioactivity associated with global fallout were small indeed, despite claims to the contrary (see section VIII). Definitive research on biological effects could only be performed in the laboratory using the types of work described in earlier chapters and to be reviewed in chapter 13. Thus, field research in the biomedical area had to be limited largely to biokinetics and was pretty much an extension of that we reviewed in chapter 11 and earlier in this chapter.^(a)

(a) Because of the low levels involved, only postulated longer-term effects of radionuclides were of importance. Acute effects were essentially out of the picture for global fallout from weapons testing.

Nationwide and worldwide fallout problems from weapons testing led also to one of the most serious conflicts between science and society seen since the arguments over evolution and the origin of man. Fueled by fears of nuclear weapons per se, by the fact that the benefits of testing (i.e., improvements in weaponry and the maintenance of "peace through strength") could not be divulged in any detail to the general public, and by fear of unknown long-term biological effects, the issue suddenly became major. As we know, it even entered a presidential campaign. A statesman-like review of these sociopolitical aspects of the problem was presented by Commoner (1958) at a symposium on the Social Aspects of Science at a meeting of the American Association for the Advancement of Science.

Important as they are, little else can be said here on these aspects without straying too far from the purposes of a book devoted to biomedical research.

Fortunately, the entire field of global fallout has been exhaustively documented. The many lengthy hearings held under the auspices of the Joint Committee on Atomic Energy of the U.S. Congress are almost overwhelmingly complete. The 1955 print was 60 pages in length; the 1957 print 2,216 pages, the 1959 print 2,618 pages, etc. If these mammoth volumes were easily available, we would need no other literature citations except for work abroad. However, the hearings are not generally available and something more digestible is needed anyway. A succinct and readable distillation can be found in chapter 14 of Eisenbud's book, *Environmental Radioactivity* (1973). The special problems of transuranic elements in worldwide fallout are summarized well in Hanson's book, *Transuranic Elements in the Environment* (1980).

Between these in volume and in conciseness are the reports of the U.S. National Academy of Sciences' several committees on the Biological Effects of Atomic Radiation (BEAR) done specifically around the problems of fallout (NAS-NRC 1956, 1961, 1963); the report of the Medical Research Council of the United Kingdom (MRC, 1956), also written entirely around the problems of fallout; and the several reports of the United Nations Scientific Committee on the Biological Effects of Atomic Radiation (UNSCEAR 1958 et seq.). In addition, there were, of course, many symposia and hundreds of individual papers on specific aspects.^(a)

With such a plethora of documentation, there is little point in delving deeply into individual facts. Instead, we will concentrate on the historical progression of thought and on the institutions and ideas most prominently involved in the field phases.

B. The Physical Events and Measurements

1. The Events

As described exhaustively in documents such as Glasstone and Dolon's *Effects of Nuclear Weapons* (1977) and Eisenbud's *Environmental Radioactivity* (1973), there are three major classes of fallout: local, tropospheric, and stratospheric. We are concerned here only with the latter two. We saw in earlier sections of this chapter that local fallout is extremely important near to and within up to a few hundred miles of a large burst. Events in the kiloton range inject much radioactivity into the troposphere in which it can be carried over considerable

(a) Selected listings of the contents of BEAR reports and of the entire MRC report are given at the end of this chapter as notes 2 and 3.

distances, e.g., across the continental United States. It descends gradually by convective mixing, or rapidly in rain or snow. The retention time in the troposphere is dependent upon the initial particle size distributions and the presence or absence of storms. It is short in relation to stratospheric retention. With multiple kiloton shots, the tropospheric fallout could add up to large doses of external gamma radiation and significant beta-particle effects. However, for our testing activities, the subject of this section, the tropospheric contribution is small (about 5%) compared to that from the stratospheric reservoir.

Eisenbud cites figures indicating that almost all of the debris and radioactive fission products enter the stratosphere from bursts with a yield of more than about five hundred kilotons. Thus, a large part of the megaton-yield test debris enters the stratosphere. Residence time is not constant and is difficult to establish with certainty. However, by the use of stratospheric sampling with balloons (Project Ashcan), and later by very high-altitude U-2 aircraft, and unique labeling of some of the U.S. tests in the Pacific with ^{185}W , both an approximate inventory and a retention half-time in the stratosphere could be estimated.

In early years, both AEC and UNSCEAR estimated mean residence time in the stratosphere at 5 to 7 yr and the inventory at between 4.3 and 5.5 MCi of mixed fission products. By 1959, the inventory figure was revised to about 0.8 MCi and the mean residence time to twelve to eighteen months. The 1962 estimate was still lower because of the cessation of atmospheric testing and consequent reduction of input and removal by both radioactive decay and exchange to the troposphere. The calculated residence time was 0.7 ± 1 yr.

These figures, of course, have considerable bearing on the prediction of biological dose. Even the extremes of the range do not, however, change the principle that with stratospheric fallout the biological problems are largely the deposition of radionuclides in tissues and organisms and their possible long-term effects, not external radiation doses. Herein lay much of the public apprehension. It was easier to give fairly confident estimates of the external doses from early fallout and their possible effects than to be confident about the risks of cancer from radionuclides in the body some decades hence.

The rest of the physical phenomena can be studied in depth in the references cited. Suffice it to say here that much fine research was done in establishing the behavior of the components of fallout, including the use of the presence of radioactivity as a convenient tracer for the behavior of the components of fallout in the atmosphere, hydrosphere, and lithosphere.^(a)

2. The Measurements

a. The Sunshine Project

Relatively early, the AEC established a secret project to study the fallout that might be expected in a nuclear war. This was a particular interest of AEC Commissioner Willard Libby. The Rand Corporation assembled a group of scientists at Santa Monica, California, to organize the effort. The sunny site of this meeting led to the appellation, "Sunshine Project." Originally there were two laboratories involved, Dr. Libby's laboratory at the University of Chicago and the Lamont Geological Observatory of Columbia University at Palisades, New York.

(a) For meteorological aspects see, for example, discussion by Wexler et al. (1956) at the first Atoms for Peace Conference; the NAS-NRC BEAR reports in 1956 and 1960 (NAS-NRC:1960); also Machta, List, and Hubert (1956).

Gradually, many other AEC laboratories were drawn in, and the program became elaborate and far-flung. Reports appeared first from the Rand Corporation and then as AEC documents. Classification remained in force on much of the work until the pressures of the Congressional hearings and other factors brought the activity into a more open arena.

It was necessary early to pick a few elements out of the welter of fission products and concentrate attention on them. Particular emphasis was placed on ^{90}Sr as a bone seeker of long half-life and considerable abundance in fission and, thus, in fallout; ^{137}Cs , a soft-tissue seeker of comparable abundance; and ^{131}I for reasons already obvious from earlier discussions. The Sunshine Project became especially interested in strontium (both ^{89}Sr and ^{90}Sr) and devised a unit for its concentration, known as the "Sunshine Unit," which was based on the amount of strontium per unit of calcium, since in most systems of interest strontium resembles calcium in its behavior and could be regarded, in a sense, as a diluent to a large calcium pool. Expressed as picocuries (or micro-microcuries) of ^{90}Sr per gram of calcium, one "Sunshine Unit" equaled $1\ \mu\text{Ci/g}$ calcium. In much of the early reporting, strontium data were reported in this unit or in another we will meet presently, the Maximum Permissible Concentration (MPC) Unit.

As the fallout controversy heated up, many observers reacted negatively to the term "Sunshine" for the project and the unit. Not knowing the rather innocent origin of the term, it was interpreted as an attempt by the government to cast the subject in spuriously bright terms, even to imply that fallout was "good for you." The unit was eventually renamed the "Strontium Unit," and the project gradually lost its identity as the participants grew in number and variety.

Key open-literature references to the Sunshine Project and the ideas of Willard Libby are concentrated in 1956. In a paper to the National Academy of Sciences (Libby 1956c), he emphasized soil and biological concentrations of strontium, and coined the term "MPC Unit." This unit was derived from the fact that the MPC of ^{90}Sr in the body, based on toxicity relative to radium (see section VII), was $1\ \mu\text{Ci}$. Since the body contains approximately 1,000 g of calcium, "1 MPC Unit" became $1\ \mu\text{Ci } ^{90}\text{Sr/kg}$ calcium. The amounts found were always much lower, on the order of one one-hundredth or less. The Sunshine Unit, later Strontium Unit, was equivalent to 0.001 MPC unit or 2.2 disintegrations per minute (dpm) $^{90}\text{Sr/g}$ calcium. For some time, strontium was reported in fractions of MPC Units, apparently as a convenient reminder of how far below the maximum permissible level the incoming figures were. This, too, raised a few eyebrows and was considered confusing in the long run, especially since it was tied to a unit, the MPC, that was subject to change.

In a later paper, also in the *Proceedings of the National Academy of Sciences*, Libby summarized current research and, among other things, showed graphically the total ^{90}Sr fallout in specific cities such as Chicago in 1955 and Pittsburgh in 1955–1956 (see figures in the section on strontium), which showed a gradual rise for Chicago, a somewhat steeper rise for Pittsburgh (Libby 1956a).

In a paper published in *Science* (Libby 1956b), a general analysis was made of the results of Project Sunshine with the conclusion "...these local precautions should be entirely adequate and the worldwide health hazards from the present rate of testing are insignificant."

By 1959, Chairman John A. McCone of the AEC announced that there would be regular quarterly releases of all fallout information (McCone 1959). These releases included work from HASL, the various AEC contractors, and many data

from PHS. The first such report included information on *plutonium* collected by Isotopes, Inc. of Westwood, New Jersey, the beginning of a long continued facet of the fallout operation. Mr. McCone emphasized that nothing would be held back so long as he was chairman of the AEC,^(a) quite a shift from the classified status of the early Sunshine reports:

b. General Governmental Involvement

By the time of the 1957 Congressional hearings, the gummed paper tray network described earlier as a brainchild of Eisenbud and colleagues at HASL in New York and an extensive air sampling network were in operation. Reports were made by many AEC groups, both in-house and contractors, by the Naval Research Laboratory, the NRD, the U.S. Department of Agriculture, the Weather Bureau, and by the PHS. The data covered the world in points of origin and involved thousands of pages of detailed documentation. For many years, the PHS issued a monthly summary of the concentrations of many radionuclides in several media as a part of a journal, *Radiological Health Data*. In terms of raw data acquisition, there has probably never been a project that produced any more than these fallout measurements:

The Congressional hearings are the best single source for raw data. Other sources are better for consolidation and interpretation. An early review that preceded even the open literature reports of Libby and the Sunshine Project is one prepared by Howard Andrews (1955). Andrews, a PHS officer, represented the PHS at a large number of tests as described in a previous section. As a member of the Test Managers' Advisory Panel (see earlier sections) he was able to see the broad picture. He reviewed mechanisms of fallout formation, its dynamics, possible effects and radiation dosages and the fact that only 0.5- to 5- μ diameter particles are of any significance for inhalation. He concluded, in the light of the conditions of the day, that the testing program was justified by the defense effort but urged very careful controls.

By 1965, a book-length summary gleaned from a conference at Germantown, Maryland, and sponsored by the Fallout Studies Branch of the AEC's Division of Biology and Medicine (Klement 1965)^(b), mustered nearly one thousand pages, all concerned with physical and chemical measurements of importance to biology and medicine. The last seventeen papers involved biological materials. The table of contents of this volume is shown as note 1 at the end of this chapter. Perusal of this should give a reasonable sample of the variety and breadth of the investigations. And remember, this was only the work pertinent to a branch of AEC concerned primarily with biomedical problems.

c. International Activities

To have extensive coverage of the world for collection of fallout, nearly every nation with scientific capabilities had to play some role. We have already cited

(a) That is, presumably nothing of importance to biological or medical evaluations. The exact statement was, "... I assure this committee most emphatically and unequivocally that so long as I am Chairman of the Atomic Energy Commission I shall not be a party to the suppression or distortion of any information bearing on the safety and health of the American public."

(b) This author is indebted to Dr. Kermit Larson, Seattle, Washington, for providing a copy of this somewhat scarce document.

the extensive U.K. report that covered the entire problem. Not only the United Kingdom, but Argentina, Australia, Austria, Canada, Chile, Denmark, the Federal Republic of Germany, Finland, France, India, Italy, Norway, the Soviet Union, Sweden, Switzerland, Taiwan, United Arab Republic, and many others had extensive sampling networks. Other countries cooperated by allowing collection of samples within their territory. Before the activities ceased, there were even extensive measurements in the Arctic and useful collections from the Antarctic.

The UNSCEAR reports provide ample summaries of the worldwide data and extensive literature citations.^(a) In addition, specific mention is made of work from France (Pellerin et al. 1967) Japan (Izawa, Tsubota, and Nagai 1961), and the Soviet Union (Petrov et al. 1966).

d. Representative Findings

We will review here, very briefly, some of the typical data obtained that pertained to eventual accumulation of fallout radionuclides in the tissues of man, in other components of the biosphere, and in food. We will emphasize the earlier findings and developments.

Among the early unclassified documents is a review of "Radioactive Dust from Nuclear Detonations" prepared by Eisenbud and Harley (1953), which presented results from the fixed (121 stations) and mobile monitoring programs coordinated by HASL with assistance from the U.S. Weather Bureau and DoD. (The mobile teams concentrated on the NTS environs.) The numbers were gross activities reported in disintegrations per minute per square foot. The maxima for the fixed stations were 4,500 at Concordia, Kansas; 3,400 at Norfolk, Nebraska; and 3,600 at Milwaukee, Wisconsin. There was one reading over 2,000 dpm/ft² in upstate New York (in Dexter). Most of the readings in the eastern states were lower. The mobile teams found much higher depositions, but these were more local than nationwide or worldwide fallout. It seems likely that this report, along with its references to earlier published work, was one of the earliest to call attention to the potential biomedical importance of nationwide fallout.^(b)

Three years later, Eisenbud and Harley (1956) updated the figures and expanded them to a worldwide basis. They used largely gummed film and high-walled pots for collection. There were seventeen locations in the continental United States and sixty-two in other parts of the world. They reported mixed fission product activity, ⁹⁰Sr, and gamma dose. The units were millicuries per square meter for the radionuclides and mrad for the gamma dose. The change of units makes comparison to the earlier reports or to the Sunshine Project units difficult. However, the authors comment that all figures are far below those needed to develop a dose approaching the maximum permissible (see section VII).

In the next year, Eisenbud (1957) described the global distribution of ⁹⁰Sr from nuclear detonations with regional summaries of deposition, an estimate of the stratospheric reserve, and the relations between amounts in soil and in milk (more later).

(a) The reader interested in specific countries should consult the list of reports received by the Committee that appears at the front of each UNSCEAR report.

(b) The Sunshine Project was, of course, gathering data in this period, but its reports remained classified or, at least, not generally available until the 1956 Congressional hearings and Commissioner Libby's several summaries.

By this time, the Libby papers had begun to appear, and all the detail was made available in the 1957 Congressional hearings. Air filter data were also added. An example of the gradual increase in ^{90}Sr deposition at two locations (Chicago and Pittsburgh) and worldwide rates are shown in figure 12.15A, B, and C. The upward trend seen in figure 12.15A and B was one of the reasons for the growing concern over worldwide fallout. Other graphs (like figure 12.15C) do not show such a distinct trend and have much wider ranges for the points. An example of the air sampling data, taken also from a relatively early

FIGURE 12.15A. (Right) Chicago fallout in 1955. (Redrawn from Libby 1956a.)

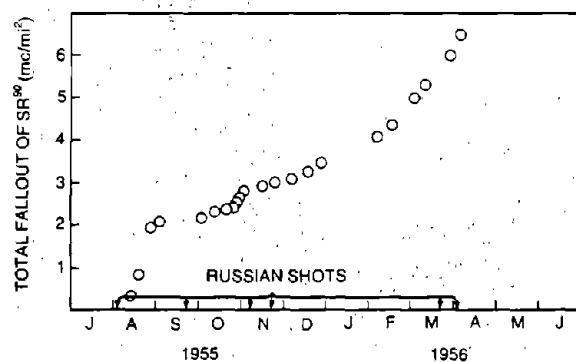
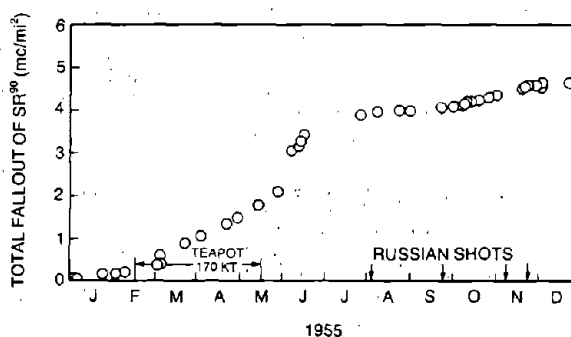
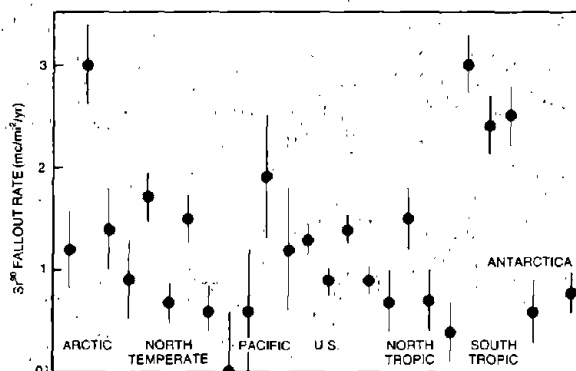


FIGURE 12.15B. (Left) Pittsburgh fallout in 1955-1956. (Redrawn from Libby 1956a.)

FIGURE 12.15C. (Right) Worldwide Sr^{90} fallout rates. September-December, 1954 (gummed paper at 63% efficiency except Antarctic value, which was snow). (Redrawn from Libby 1956c.)



report by Libby for air in Washington, D.C., is given as figure 12.16. These air sampling procedures were continued over many years for monitoring of both local and global fallout. A typical portable sampler and generator used by the PHS for its offsite surveillance, but not greatly different from those used for more general measurements, is shown in figure 12.17.

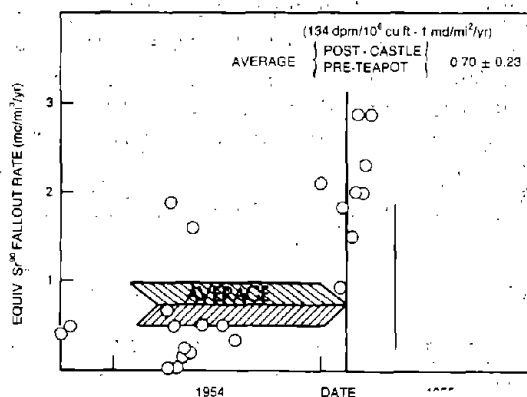
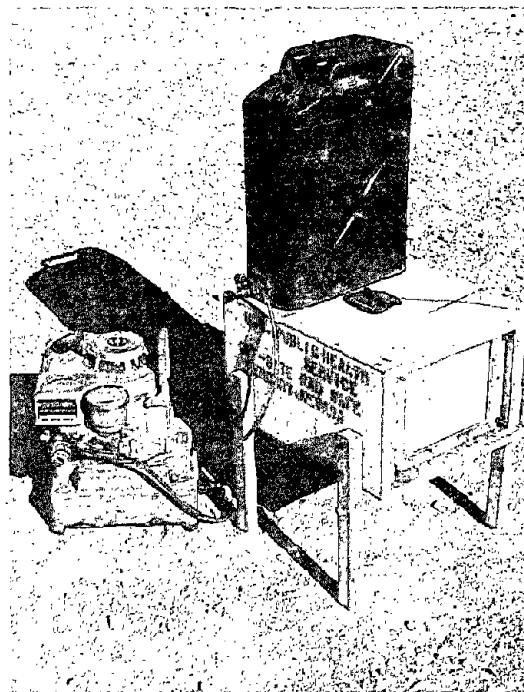


FIGURE 12.16. (Left)
Strontium-90 in air, Washington,
D.C. (Redrawn from Libby 1956c.)

FIGURE 12.17. (Right) Air sampler and portable generator. (Courtesy of Dr. Melvin Carter, Georgia Institute of Technology.)

The National Air Sampling Network of PHS began in 1953 and was set up to detect trends in the nature and extent of air pollution in the United States. The analysis of radioactivity from fallout was essentially an addition to its original purpose. Beginning with 17 communities, it expanded rapidly so that in three years there were 66; by 1959, 117 sampling sites, 66 in large cities, 51 at nonurban sites. Sampling was also done on an intermittent basis at additional smaller cities so that the grand total was 236 sites. The samples were collected about once in two weeks using a twenty-four-hour sample period, which was found to be as valid statistically as continuous sampling over the entire period and much easier to maintain. The 1959 Congressional hearings give many tables of gross beta activity in air over a



five-year period (pp. 173-185) but present no interpretation of their biological significance except for the obvious fact that they are mostly below $100 \mu\text{Ci}$ (μCi) per cubic meter.

Alexander, Hardy, and Hollister (1960) gave a convenient summary of radioisotopes in soils from worldwide fallout at the symposium described earlier on radioisotopes in the biosphere at the University of Minnesota. Alexander was at the U.S. Department of Agriculture, Hardy at HASL, and Hollister at AEC Headquarters. The sampling was both general and specialized along contours of moderate to heavy rainfall. The variation with latitude is strikingly demonstrated in figure 12.18. Similar variations with latitude were seen in samples from the troposphere, the stratosphere, and in the oceans.

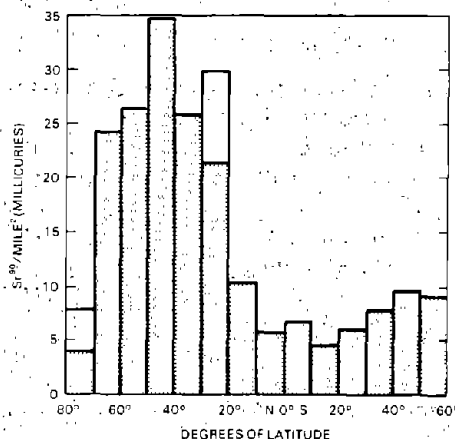


FIGURE 12.18. Millicuries of Sr^{90} per square mile in soil, 1955. (Redrawn from Alexander, Hardy, and Hollister 1960. (a) Reprinted with permission of the University of Minnesota-Twin Cities, Minneapolis, Minnesota, copyright 1960.)

As we saw earlier, the chemistry of sea water produces differences between the cadre of radionuclides remaining in the marine environment compared to the terrestrial. Also, relatively small-sized particles from fallout may remain in surface or near-surface layers of the sea and be moved about by currents. Obviously, a large portion of global fallout has reached the sea, but measurements are much more difficult than for equivalent land areas. Only special expeditions, such as those described in connection with the Pacific tests, have done much more than spot-sample the oceans. Revelle gives a succinct summary of relatively early findings in the 1957 Congressional hearings (pp. 523-535). The story as it progressed can be seen in the NAS-NRC reports on marine radiocology. No startlingly different phenomena have appeared regarding fallout in the oceans. However, we must always remember the potential for significant concentration factors for radionuclides from worldwide fallout in marine organisms; also the fact that because of its relatively high ^{40}K content, the overall specific activity of radionuclides in the oceans may be different from that in terrestrial systems.

C. The Biomedical Aspects of Global Fallout

It was clear from the physical events and measurements that a strenuous effort should be mounted both to determine the amounts of radionuclides from

(a) The open areas in the bar graphs for 70° - 80° and 20° - 30° north latitude represent contributions from potentially anomalous areas. Details are given by the author on p. 8 of the cited reference.

fallout in components of the biosphere and to support reasonable guesses as to their biological significance, i.e., the dose to humans and other organisms. The ubiquitous problem of the long-term effects of very low levels of radiation presented a major obstacle. In the early times, when so much less was known about the biological effects of radiation, there was considerable difficulty in interpretation. We will examine in this section a few of the early and later findings and then summarize the efforts to decide on their biomedical significance.

1. Radionuclide Content of Biological Materials

a. Strontium

Despite its origin in the physical sciences, the Sunshine Project produced fairly copious quantities of information on the concentrations, particularly of ^{90}Sr , in materials of biological significance. In the papers by Libby, already cited, and in an address to the American Association for the Advancement of Science on Friday, October 12, 1956, in Washington, strontium content of human bone, human stillborns, calf bones, and sheep bones was given from work done at Chicago and the Lamont Laboratory. The contents were given as fractions of the MPC Unit defined above. They showed a slowly rising tendency with time between 1953 and 1956, but all the human bone data are in the range of 0.001 to 0.002 MPC Unit, mostly below 0.001, while the figures for calf and sheep bones were in the range of 0.01 to 0.02 MPC Unit. Amounts in Wisconsin cheese ranged to 0.01 MPC Unit; with most of the figures less than 0.005; in Swiss cheese, 0.01 MPC Unit or above; in Chicago milk, from 0.001 to about 0.008 MPC Unit with the majority below 0.005 MPC Unit; and "foreign milk" (many countries including some in the Southern Hemisphere) seldom above 0.003 MPC Unit. The reports were generous with details of both specific figures for each sample location and methodology.

In 1957, the Lamont group (Kulp, Eckelmann, and Schulert 1957) felt ready to focus on strontium in humans in an independent publication. They produced radiochemical analyses (over fifteen hundred samples) of ^{90}Sr in bone from seventeen locations worldwide, arranged for largely through personal contacts and friendships. They concluded that the worldwide average at the time was about $0.12 \mu\text{Ci/g}$ calcium (note the use of micro-microcuries rather than MPC Units) and that this was about one-ten-thousandth of the then-accepted maximum permissible concentration for the body content of humans. There was surprising uniformity in the samples from all stations except those in Chile and Brazil. This indicated that the stratospheric exchange phenomena had already "swamped" the tropospheric concentrations from both Nevada and Soviet tests. They demonstrated clearly an effect of age seen but not as completely in some of the earlier work. Young children had three to four times more ^{90}Sr per gram of calcium in their bones than did adults, which helped to concentrate attention on the young just as occurred for iodine in the thyroid. Finally, it was clear that there could be large deviations from the mean for a given locality, e.g., to as much as ten times the average. This was attributed to diet and helped to stimulate still further investigations of dietary content of ^{90}Sr .

The Los Alamos Health Group sprang into action relatively early in the worldwide fallout work, perhaps because of their close contacts with the tests and the weapons makers. Langham was active in the 1957 and 1959 Congressional hearings (more later). A convenient review of his findings and ideas appeared in the first volume of the then-new journal, *Health Physics* (Langham

1958). He and his colleagues devoted considerable attention to possible future levels of ^{90}Sr in the biosphere and in humans with or without further testing (Langham and Anderson 1958). His postulated average maximum levels in the world population are shown in table 12.14.

TABLE 12.14. Postulated Average Maximum Equilibrium Sr^{90} Bone Levels in the World Population (pc/g bone Ca)

Region	Mid-1957		About 1963*		About 2050†	
	Ecol. Data	Bone Data	Ecol. Data	Bone Data	Ecol. Data	Bone Data
United States	3.1	1.7	3.5	1.9	31	17
North temperate latitude	3.2	1.7	3.6	1.9	32	17
South temperate latitude	0.6	0.5	0.7	0.6	6	5
Rest of world	0.8	0.3-0.5	0.9	0.5-0.8	8	3-5
World average‡	(2.8)	(1.5)	(3.1)	(1.7)	(28)	(15)

* Assuming no more weapons tests.

† At equilibrium with a continued test rate of 10 MT equivalents of fission per year.

‡ Population weighted average.

Source: Reset from Langham 1958. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1958.

With a recommended maximum level in the general population of one-tenth of the occupational limit of $1\ \mu\text{Ci}$ body burden (primarily skeletal) and the fact that the average adult human skeleton contains 1,000 g of calcium, the maximum permissible level of $0.1\ \mu\text{Ci}$ of ^{90}Sr is $0.1\ \mu\text{Ci/kg}$ calcium, or $100\ \text{pCi/g}$ calcium, or 100 Sunshine Units. The predicted levels to 1963 with no further testing (table 12.14) are all less than one-tenth of this figure. They became appreciable fractions of $100\ \text{pCi/g}$ calcium by the year 2050 if testing were to be continued at 10 MT equivalent of fission per year. We will return to these matters.

To save precious space, we will skip many calendar years; hundreds of man-years of work, and millions of dollars of financial input and go to the picture in retrospect as shown by UNSCEAR (1977). Composite results over a decade and a half for dietary ^{90}Sr for New York City and for Denmark are shown in figure 12.19A and B. The amounts in bone are given in huge tables in the report. A glimpse of the picture can be seen in figure 12.20, which compares the Northern and Southern Hemispheres over a twenty-year period.

The consequences of all this are given by UNESCO in terms somewhat different from those in earlier work, viz., as an integration of the radiation dose known as dose commitment (chapter 16 and literature cited therein). The figures, given in millirad, are shown in table 12.15. These figures are a comfortably small fraction of the allowable population dose commitment. However, we should remember that ^{90}Sr is only one of many radionuclides plus small amounts of external radiation contributing to the total dose from global fallout and also that even now (mid-1980s) there is controversy over what the allowable dose commitment to the population should be or should have been.

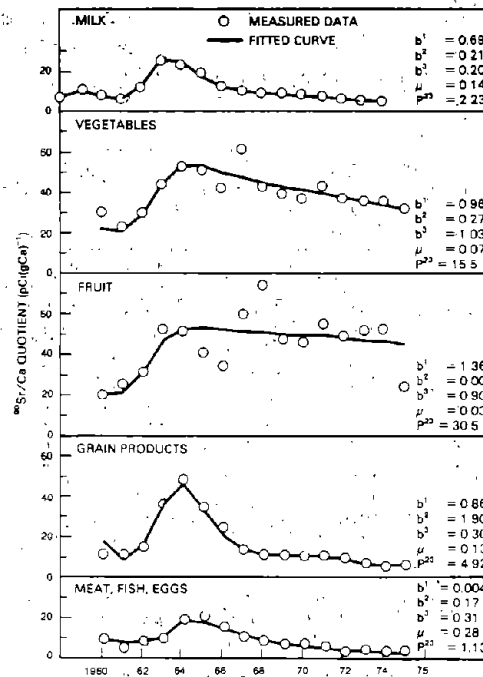
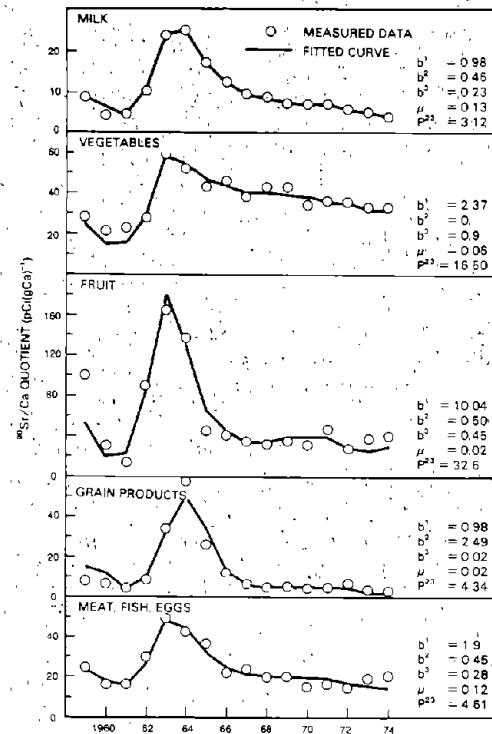


FIGURE 12.19A. (Left) Variation of ^{90}Sr in various diet components in New York City, 1959-1975. The unit for the parameters b_1, b_2, b_3 is $\text{pCi}(\text{gCa})^{-1}$ per mCi km^{-2} . The unit for parameter μ is y^{-1} . The unit for the transfer factor P_{23} is $\text{pCi y}(\text{gCa})^{-1}$ per km^2 . These transfer functions relate the amount in fallout to the amount in diet and are given in more detail in the UNSCEAR report. (Modified slightly from UNSCEAR 1977.)

FIGURE 12.19B. (Right) Variation of the ^{90}Sr in various diet components in Denmark, 1960-1974. The unit for the parameters b_1, b_2, b_3 is $\text{pCi}(\text{gCa})^{-1}$ per mCi km^{-2} . The unit for parameter μ is y^{-1} . The unit for the transfer factor P_{23} is $\text{pCi y}(\text{gCa})^{-1}$ per km^2 . These transfer functions relate the amount in fallout to the amount in diet and are given in more detail in the UNSCEAR report. (Redrawn from UNSCEAR 1977.)



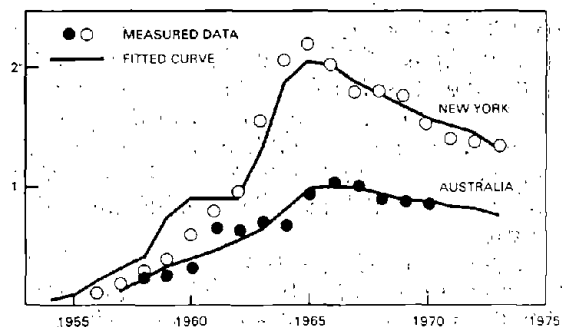


FIGURE 12.20. (Left) Variation of ^{90}Sr in bone in Australia and in New York City, 1955-1975. (Redrawn from UNSCEAR 1977.)

TABLE 12.15. Dose Commitments to Bone Tissues from ^{90}Sr Produced in All Nuclear Explosions up to the End of 1975 (mrad)

Tissue	Northern Hemisphere		Southern Hemisphere	
	Temperate Zone	Population-Weighted Average	Temperate Zone	Population-Weighted Average
Bone marrow	85	56	24	17
Endosteal cells	116	77	33	24

Source: Reset from UNSCEAR 1977.

b. Cesium

There was considerable interest in the possible accumulation of ^{137}Cs from global fallout because of its high yield, moderately long half-life, and localization in soft tissue. It contrasts to the strontium isotopes since the latter are primarily bone seekers and the hazard from them is primarily that of bone cancer and leukemia from irradiation of bone marrow. By contrast, cesium could produce both somatic and genetic effects. (We have already seen its key importance in the long term to local fallout from the Bikini tests.)

A timely summary of ^{137}Cs contamination of the biosphere came from Los Alamos (Langham and Anderson 1958, 1959). Also, there was considerable information presented at the earlier Congressional hearings. Indeed, partly because of the potential for irradiation of gonadal tissues by cesium and other more or less generally distributed radionuclides, the Congressional hearings and other publications of the late 1950s contained dissertations on the potential genetic hazards of radiation and fallout (see, for example, Glass 1957).^(a)

Langham and Anderson estimated a surface deposition of cesium in the north central population belt of about 36 mCi/mi² and a stratospheric reservoir of 4.2 MCi. These are higher than the figures for ^{90}Sr , which were 20 mCi/mi² and 2.3 MCi, respectively. In general, the cesium/strontium activity ratio in fallout is above 1. This does not necessarily mean that cesium presents a greater hazard than strontium. Although the isotope of most concern, ^{137}Cs , has a physical half-life of many years, in fact slightly longer than ^{90}Sr , its retention in the body is

(a) These concerned primarily external sources of radiation.

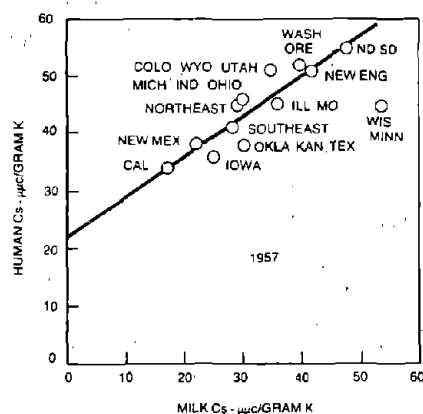
much shorter (biological half-life of ^{137}Cs is about 70 days in whole body and 140 days in bone, compared to then-current figures of 1.3×10^4 days in whole body and 1.8×10^4 days in bone for ^{90}Sr). It is the potential irradiation of radiosensitive soft tissues, including gonad, that causes cesium to be of any concern.

Cesium is chemically similar to potassium and is similarly metabolized in the body. Therefore, data on incorporation of cesium into the biosphere have tended to be given as ^{137}Cs /potassium ratios, much like the ^{90}Sr /calcium ratios. Cesium enters many foods, including milk.

Early in 1956, the Los Alamos Laboratory began an extensive survey of the ^{137}Cs /potassium ratio in milk supplies throughout the United States. Also, Los Alamos and many other laboratories took advantage of the 0.661-MeV gamma ray from ^{137}Cs to measure the body contents of this isotope in humans and other components of the biosphere. The levels in milk, while they varied, averaged in the late 1950s about 32 pCi (μCi)/g potassium. Highest values were in northern Wisconsin, Minnesota, and North Dakota. The rest of the samples averaged about 20 pCi/g potassium.

Amounts in people were reported as about 41, 44, and 54 pCi/g potassium in the U.S. population in 1956, 1957, and 1958, respectively. The correlation between amounts in people and amounts in milk was very positive, which is illustrated in figure 12.21, taken from the Langham and Anderson papers.

FIGURE 12.21. Correlation of Cs^{137} levels in the U.S. population with levels in milk. (Redrawn from Langham and Anderson 1959. Reprinted with permission of Pergamon Press, Ltd., Elmsford, New York, copyright 1959.)



There was a wide difference among species in the whole-body retention of cesium (^{134}Cs and ^{137}Cs) as seen in the laboratory work of Richmond et al. at Los Alamos, cited in chapter 8. The retention half-times were 1.5 days in the mouse, 6 days in the rat, 19 days in the monkey, 25 days in the dog, and 110 days in man. These differences bespeak the importance of doing field- and survey-type work on people. (a)

The amounts of ^{137}Cs found in people by Langham and Anderson were used to calculate an average radiation dose to bone marrow over seventy years and the possibility of genetic effects. If testing were to continue at a rate of 10 MT of fission per year, the bone marrow dose came to 500 mR. The calculation of genetic changes was, based on the same assumption regarding continuation of testing, 30 to 50 R as the doubling dose for mutations and no threshold for the

(a) Remember the problems Robley Evans had with radium in the rat versus humans described in chapter 1.

genetic response. The increased mutation rate from biospheric contamination with ^{137}Cs was judged to be about 0.5% to 1%.

Interestingly, the potential for leukemogenesis for ^{137}Cs and ^{90}Sr was judged to be about the same if both radionuclides entered the body via soil contamination and subsequent uptake by plants. By contrast, ^{137}Cs was considered only one-fifth as likely to cause leukemia as strontium if entry was by direct contamination of vegetation. Such influences of the pathway were commonly found and stimulated much additional work in both field and laboratory (chapters 13 and 15). Exquisite detail concerning both the levels and importance of cesium isotopes is contained in the several hearings (note especially 1957, p. 751-765).

The Argonne National Laboratory brought its whole-body counter to bear on measurements of cesium in people and also mounted a long-term study of its deposition rate, levels in food, and dose to humans, primarily through the work of P. F. Gustafson. This work continued well into the 1970s and is summarized conveniently by Eisenbud (1973, p. 380 et seq.), along with correlative work at HASL. In October 1968, it was estimated that the Chicago diet introduced 12,300 pCi of ^{137}Cs per year, with milk contributing the largest single portion.

UNSCEAR (1977) estimated that ^{137}Cs absorption had produced a fifty-year dose commitment of 62 mrad in the north temperate zone, 18 mrad in the south temperate zone, and a world population average of 38 mrad.^(a)

An important corollary of the close linkage between cesium and potassium is seen when uptake occurs from soils deficient in potassium. In this case, the cesium may be concentrated to a much greater extent in dietary items. For example, Broseus (1970) reported ^{137}Cs contents in milk from ten to one hundred times normal for a given deposition in areas of Jamaica with potassium-deficient soils.

In the following years, whole-body counters throughout the world followed the ^{137}Cs content of humans and the biosphere. As we did for strontium, we will again skip many years and look at the picture after sufficient time had elapsed to permit a retrospective as well as a prospective view.

The Los Alamos group followed through with whole-body counter measurements of the normal New Mexico population over the period 1956-1977 (Thomas, Anderson, and Richmond 1978; an abstract by Furchner, Wilson, and Richmond 1975; and Richmond and Furchner 1967). The reports build upon other work, cited therein, from several laboratories, including especially Cincinnati (Lewis et al. 1976), Argonne, and Utah (Lloyd and Rundo 1976). The gross trend with over forty whole-body counts per year is seen in figure 12.22, taken from the Los Alamos work.

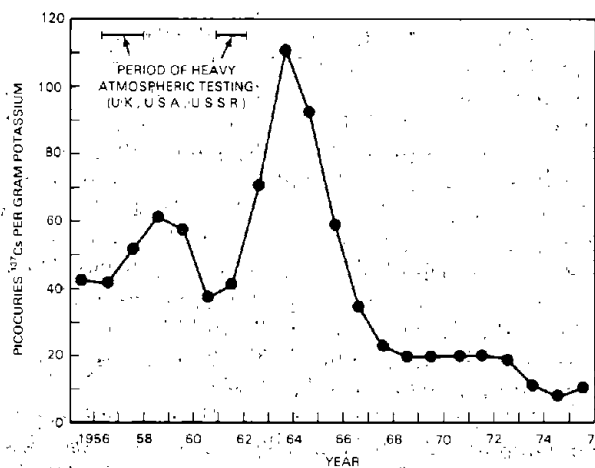
It is obvious that the concentrations reported in 1958 were considerably exceeded by 1964,^(b) while by 1977, the body contents were about one-fifth of those in the 1950s.

These retrospective analyses pointed to a pronounced time lag in the body burden after each large series of tests. It seemed to be about two years for both the increase and the decrease. Since the retention time of ^{137}Cs in humans is much less than two years, this phenomenon must reflect changes in environmental

(a) It should be noted that, although cesium contributes little to the external radiation dose from fresh fallout; its long physical half-life means that residual cesium contamination on the ground may contribute a considerable portion of the external dose after the shorter-lived radionuclides have decayed away.

(b) The highest average in the United States was 180 pCi/g potassium in 1964, reported by Shukla, Dombrowski, and Cohn (1973) from Brookhaven.

FIGURE 12.22. Whole-body concentration of ^{137}Cs in normal New Mexico population. (Redrawn from Thomas, Anderson, and Richmond 1978.)



concentrations and their effect on the dynamic equilibrium in people. Lewis et al. (1976) summarized the calculated biological half-lives of ^{137}Cs in humans and pointed out the very large range of values. Lloyd and Rundo (1976) addressed this apparent anomaly as another example of environmental transfer effects. They urged that cognizance be taken of the fact that there are two half-lives in these situations, that resulting from physiological processes in people and another resident in the environmental behavior of the radionuclide. They are, of course, separable only by independent laboratory-type measurements.

c. Iodine

As related earlier, it was Van Middlesworth working at Memphis, Tennessee, who first reported in open literature the appearance of radioactive iodine in fresh animal thyroids (1954). This bore more on nationwide than on worldwide fallout, even though it contained samples from both east and west coasts. In 1956, Van Middlesworth gave data on the ^{131}I content of 175 human cases and 1,044 animals over the period from October 1954 to February 1956 (Van Middlesworth 1956). The United States, Canada, England, Germany, and Japan were included in the study. Because of the relatively short radioactive and biological half-lives of ^{131}I , the concentrations show a markedly sawtoothed relationship to time, rising and falling by factors of ten or more over periods of a few months. They thus reflected the tests or series of tests more faithfully and more quickly than either strontium or cesium. Indeed, this rather rapid response with time soon led to interest in iodine concentrations as bellwethers for impending changes in general levels of fallout radioactivity, especially any rapid build-up in the biosphere that might serve as a marker for other radionuclides that were much less easily measured by the techniques of the day.

As described in connection with local and regional fallout, Van Middlesworth used methods for estimating thyroid dose derived for the conditions of the day by Dunning (1956). These considered especially the early contributions of the short half-life iodine isotopes. He calculated doses on the order of 0.15 to 0.40 rep and compared these to the 5,000- to 10,000-rep doses used to treat hyperthyroidism in people; he makes no mention, however, of thyroid cancer that now demands primary attention.

The group at the Oak Ridge Institute of Nuclear Studies (soon the UT-AEC Experimental Farm; see chapter 13), viz., Cyril Comar and R. H. Wasserman,

invested considerable effort in all aspects of iodine in fallout. An early summary done in collaboration with Army and Air Force veterinarians assigned to the laboratory (Trum, Kuhn, and Nold) was published in 1957 (Comar et al. 1957). They studied human thyroids obtained from autopsy material, mostly from persons over fifty years of age, barn-fed cattle, pasture-fed cattle, and milk from the same areas as the cattle. Their conclusions can be reviewed best by presenting the last paragraphs of their paper:

There seems to be little question that the levels of radioiodine introduced into the biological cycles by weapons tests during 1955 and 1956 are far below those that are expected to produce any observable effects. This can best be demonstrated by comparison of levels found with the official maximum permissible values and with findings on the lowest levels of radiation or of iodine-131 that could possibly have produced detectable changes. Such a comparison follows.

- 1) Average peak level observed in man, 0.005 millimicrocurie per gram.
- 2) Maximum permissible level in man for continuous exposure, 15 millimicrocurie per gram.
- 3) Estimated peak level in milk, less than 0.01 millimicrocurie per 100 milliliters.
- 4) Maximum permissible concentration in water for continuing exposure, 3 millimicrocuries per 100 milliliters.
- 5) Estimated average dose to human thyroid from radioiodine during the period January 1955 to December 1956, less than 0.04 rep.
- 6) External dose to neck area in infants and children that has been suggested as cause of later thyroid malignancy, 200 to 725 roentgens.
- 7) Dose to thyroids of sheep on daily intake of iodine-131 at which no damage was observed, 936 roentgens (3 roentgens per week for 6 years).
- 8) Dose to thyroid of sheep on daily intake of iodine-131 at which minor physiological change occurred, 3000 to 5000 roentgens (over 2-1/2 years).

Note that iodine is reported as millimicrocuries ($m\mu\text{Ci}$), i.e., $10^{-3} \mu\text{Ci}$, rather than in micromicrocuries or picocuries ($10^{-6} \mu\text{Ci}$), and as per gram of tissue since there is no analogue of iodine to relate it to, as was done for strontium and for cesium.

The PHS produced much information on iodine, both as a result of measurements from their fallout collection network and from special studies. In 1957, Arthur Wolff reported the iodine activities from small animals necropsied at veterinary clinics in Ohio and Pennsylvania and from cattle and sheep from Pennsylvania, Arizona, Ohio, and Oregon (Wolff 1957). The work was begun before the spring 1956 Pacific tests and continued into the fall of that year. There was a gradual rise in the average iodine content of the collected thyroid glands with a peak in August 1956. Thereafter the levels fell rapidly. Thus, the work proved conclusively a connection between weapons testing and iodine in the thyroid. The small domestic animals had consistently less than the grazing sheep and cattle. The activities were in the range of 0.8 to 0.0008 $m\mu\text{Ci/g}$ thyroid in the cattle, from 2.7 to 0.12 $m\mu\text{Ci/g}$ for sheep, and a maximum of 0.46 $m\mu\text{Ci/g}$ for other animals.^(a) These concentrations agree well with those from the continuing sampling program of Van Middlesworth in the Memphis area (Van Middlesworth 1954) and result in a calculated thyroid dose of "at least 42 millirep" (range 35 to 120) per week. All of the iodine concentrations in animals were considerably above those found in humans in the same areas. Further

(a) In each case, there were many measurements at or below the limit of sensitivity.

work with bovine thyroids from the Montgomery, Alabama, area (Moore, Lambert, and Mills 1964) showed still higher amounts of ^{131}I .

In addition to its work with human thyroid exposures around the NTS, the PHS looked at ^{131}I in thyroids of the general population for correlation with worldwide fallout. Two studies are cited. The first (Visalli and Goldin 1963) concerned thyroids in children in the Winchester, Massachusetts, area. It was partly experimental in that radioiodine-free diets were given to some of the children. It proved conclusively that food, especially milk, was the primary source. The other study (Wellman et al. 1965) measured ^{131}I content of thyroids in ten children in the St. Louis, Missouri, area. (The in-vivo counts were done at New York University [NYU].) The measured amounts were only about one-half those predicted from the dietary content. However, the study was too small to draw general conclusions.

The large Soviet tests in 1961 stimulated several special studies of radioiodine in milk, thyroids, etc. During the temporary moratorium on testing, the iodine isotopes had all but disappeared from the environment except for small quantities of the long-lived members. Soon after the resumption of testing, it was reported that iodine from the Russian tests was present in milk supplies in the United States. The NYU group, including Eisenbud and others who had moved over from HASL, thought it important to assay human thyroid content as soon as feasible. They embarked on a study from hospital autopsy cases in New York City and later in vivo measurements. The first measurement was made about five weeks after the resumption of testing and about ten days after ^{131}I was first detected again in New York City dairy products (Eisenbud et al. 1962). The results were insufficient to establish a distribution of thyroid doses in New York City, but it was possible to estimate dose to the most exposed portion of the population, those who drink the most milk. The integrated dose over the period of the rise and fall of the concentrations in the environment and in thyroids came out to be about 40 mrad in children who drank milk.

In general, these works indicated less significance in humans from iodine isotopes from global fallout than from many other radionuclides. UNSCEAR (1977) gives both integrated milk concentrations and calculated thyroid dose to infants from 1966 to 1974 for locations throughout the world. None are alarming because of the relative radioresistance of the thyroid, but a few approach or exceed the population limit. Later work tended to concentrate more on iodines from reactor releases and from close-in, short-term fallout, areas we have already discussed. Also, much effort was expended on transfer factors and on environmental pathways and vectors that we will meet in chapter 15.

d. Carbon-14

Both fission and fusion devices produce ^{14}C by interaction of neutrons with atmospheric nitrogen. It turns out that the two major types of weapons, as built by the United States at least, yield roughly equal fractions of escaping neutrons, or so it was thought at the time. Therefore, knowing the total energy yield, the escape fraction, and the probabilities of the reactions, those interested could estimate neutron-induced radioactivities. It was the long half-life of ^{14}C (5,780 yr) and its potential incorporation into the vital carbon cycle of the biosphere that led to concern about its presence in global fallout.

Measurements of ^{14}C in fallout and in pertinent materials are prominent in the 1957 Congressional hearings, along with discussion of its possible

significance. The findings were considerably expanded in the 1959 hearings. Since cosmic rays continuously produce ^{14}C in the atmosphere from interaction with nitrogen, the figures are usually presented as ratios of ^{14}C found to that already present in the environment (see, for example, reports from the Naval Research Laboratory in the 1957 hearings [pp. 672-675]) or as excess ^{14}C . The summary given by UNSCEAR (1977) for the period 1954-1980 shows a maximum of close to 70% above the normal amount in the troposphere in 1964 and about 20% excess in the surface ocean, peaking in late 1960s.

Carbon-14, despite its very long physical half-life and quick incorporation into the biosphere, gradually disappears into the bicarbonate and carbonate of the seas and, thus, into the carbonates of rocks and other components of the lithosphere. Hence, most estimates of possible biological effects may be too high by the extent that this sequestering process was or was not accounted for.

Relatively early in the consideration of ^{14}C , Totter, Zelle, and Hollister (1958), all on the staff of the AEC's Division of Biology and Medicine at the time, produced a broad-gauged analysis of the possible hazards of ^{14}C production. First they addressed the possible mutagenic effect of ^{14}C transmutation. (We delve into the entire transmutation problem in some detail in chapter 20. For ^{14}C , it refers to the fact that it decays to nitrogen. Thus, any molecule in which this occurs is suddenly different by some small fraction.) In the calculations of Totter, Zelle, and Hollister, it was concluded "with large uncertainty" that the transmutation effect could possibly contribute about the same number of mutations as the radiation dose from ^{14}C . This was probably an overestimate. Nevertheless, it was the possibility of mutations that captured interest for ^{14}C from global fallout and is still the prime concern.

Totter et al. estimate that bomb ^{14}C released to the date of their paper would produce a worldwide dose of 0.008 mr/yr to every individual in the population and that this would add 1 in 5,340,000 gross physical or mental defects; 1 in 1,400,000 stillbirths and childhood deaths; and 1 in 593,000 embryonic and neonatal deaths. By contrast, normal ^{14}C already present as natural background was calculated to produce 1 in 27,800; 1 in 7,400; and 1 in 1,785 in each of the categories above. This is the hazard, assuming no threshold and a linear dose-response out to about eight thousand years. As in all such calculations, the total number of defects can appear large when multiplied by the population of the world, and especially when projected forward for many thousand years.

Linus Pauling (1958), the chemist turned biologist, felt that Totter et al. and others had underestimated the hazard from ^{14}C . One of the problems seems to be the figures regarding relative production of ^{14}C by fusion compared to fission bombs. Earlier we quoted work indicating about the same escape fraction for neutrons from both types of devices. Pauling uses different figures. He calculated 13.8 kg of ^{14}C per megaton of fusion compared to 1.05 kg per megaton released in fission, or a factor of thirteen difference between the two. On this basis, he concludes that one year of testing (30 MT of fission plus fusion) would be expected to cause a total in the world population of 55,000 children with gross physical or mental defects, 170,000 stillbirths and childhood deaths, and 425,000 embryonic and neonatal deaths. These numbers are about seventeen times larger than those usually estimated for genetic effects from fallout fission products. Pauling recognizes that these are still very small percentages of the total number of such defects that would appear in the world population independent of fallout, and that they may be five times too high or five times too low.

The debate indicates how widely calculations of the effect of ^{14}C can differ. Measurements made both at the earth's surface and in the stratosphere indicated an inventory of ^{14}C of about 4.2×10^5 Ci in 1964, the peak. The individual dose commitment from ^{14}C from the end of atmospheric testing to the year 2000 has been estimated as about 13 mrem (Eisenbud 1973, p. 384). As estimated by UNSCEAR (1977), the individual dose commitments from the ^{14}C from all nuclear testing to *infinite time* are larger; e.g., 103 mrad to gonads, 124 mrad to lung, 414 mrad to bone lining cells, 455 mrad to red bone marrow, and 269 mrad for the whole-body average.^(a) About 10% of these doses would be delivered by the year 2050. While hardly devastating, these levels cannot be said to predict absolutely no significant biological effects, especially genetic changes. If they do occur they, of course, could never be identified because of the relatively high rates of spontaneous mutations and chromosome aberrations and the nonspecificity of the changes.^(b)

e. Tritium

Fairly large quantities of tritium are produced in nuclear reactions both as the result of neutron activation processes and directly in the fusion process. Most of it is in the form of tritiated water (HTO), as discussed in other chapters, and becomes a part of the biosphere. Inventories of tritium were taken early, and much attention was devoted to the residence time of both naturally produced and bomb-produced tritium in the stratosphere. The former is much longer than the latter, explained provisionally by the fact that the injected manmade tritium is, much of it, in the form of ice crystals. The movement of tritium was much used for meteorological investigations. By contrast, little attention was devoted initially to its possible biomedical significance in fallout in contrast to strontium, cesium, iodine, and ^{14}C . This contrast was based, no doubt, upon the results of the laboratory investigations, described elsewhere in this book, that indicated relatively low radiotoxicity for tritium. Also, attention was perforce directed primarily to the potential bad actors.

Nevertheless, the total inventory of tritium was large. UNSCEAR (1977) gives the world's ^3H inventory at 2,900 MCi as of 1970, the bulk of it in the Northern Hemisphere. Much has been done, particularly by the oceanographers, to determine tritium distribution in the sea, its variation with latitude and depth, and its biokinetics. The highest concentration in surface waters of the United States and Canada (eighteen U.S. rivers plus the Ottawa River in Canada) was about 5,000 pCi/l, which occurred in 1964. Dose commitment calculations have been made from these figures. Those to the whole body of the population of the United States and of the Ottawa Valley of Canada were 1.5 and 2.8 mrad per person respectively. Figures for the Southern Hemisphere averaged about 0.2 mrad.

Thus, even though the total inventory of tritium is impressive, the potential for biological effects does indeed appear small compared to many other radionuclides in fallout.

(a) Since ^{14}C is essentially low linear-energy-transfer (LET) radiation, but may have some of the properties of high-LET radiation because of its very low energy, a quality factor of two is suggested for converting these figures to millirem for genetic effects.

(b) A task group of the NCRP has reviewed the possible genetic effects of many radionuclides, including ^{14}C . (NCRP 1987).

2. Food and Water

Many examples of the amounts of fallout radionuclides in food, especially milk, have been given earlier in this chapter. However, the sampling of food and water became such a highly organized and extensive activity that we must pause briefly to review the broad picture. An early summary was produced by the Los Alamos people and helped to organize the field (Anderson et al. 1957).

As always, the volumes from the U.S. Congressional hearings give the most detail and are recommended to any reader wishing to follow specific times, places or investigations. Fortunately, the FRC developed within the Executive Branch of the federal government more or less around the problems of fallout (but also uranium miners, see chapter 3, and general standards, see chapter 16), devoted considerable attention to biomedical aspects of the fallout problem and issued important reports that provide an overview as well as specifics. Report numbers 4 (FRC 1963), 5 (FRC 1964a), 6 (FRC 1964b), and 7 (FRC 1965) all carry much information and discussion relative to food and dietary intake of fallout radionuclides.

In addition, the AEC, PHS, and later the EPA mounted and continued extensive sampling and interpretation programs, and the National Academy of Sciences entered the picture through its Committee on Food Protection of the Food and Nutrition Board (NAS 1973). In fact, the entire agricultural establishment became involved before the furor subsided. Specifics of the parts played by some of these many organizations will be clear from this and the following sections of this chapter.

a. Total Diet

By 1970 (Roeklein, Smedley, and Simpson 1970), the following formal programs were either in operation or had contributed data to the storehouse of information on the concentrations of fallout radionuclides in representative total diets:

1. AEC Health and Safety Laboratory, New York
This group was, as we have seen, among the earliest to collect information on fallout. In March 1960, it began what was known as the Tri-City Study. The cities were New York, Chicago, and San Francisco, the first two representing "wet" areas of the country, the last a "dry" area. Nineteen categories of food from an average diet were analyzed separately for ^{89}Sr and ^{90}Sr , ^{137}Cs and stable calcium. This continued through 1967. The study found that New York and Chicago were reasonably representative of "wet" sections of the country, and San Francisco of the "dry" areas, as gauged by checks of other localities.
2. The U.S. Public Health Service, Bureau of Radiological Health—Radionuclides in Institutional Total Diet Samples (1961–1967)
Monthly samples were collected from boarding schools at different economic levels to represent a seven-day diet for children aged nine to twelve and teenagers aged thirteen to eighteen. Analyses were made for ^{89}Sr , ^{90}Sr , ^{137}Cs , ^{131}I , ^{144}Ce , ^{140}Ba , ^{65}Zn , ^{40}K , ^{226}Ra , and stable calcium. This was continued until 1969 under the Food and Drug Administration (FDA).
3. Consumers Union under Contract to the U.S. Public Health Service (1959–)
This nonprofit organization became deeply involved in the biomedical implications of the fallout from weapons testing. They analyzed complete diets of teenagers for two-week periods in twenty-four cities doing, via contracting laboratories, the same radionuclides as in the PHS survey.

4. U.S. Food and Drug Administration—May 1961–November 1969
Total diet samples were collected quarterly from nine FDA districts. Aliquots were analyzed for ^{137}Cs by gamma-ray spectroscopy and for ^{90}Sr by beta-particle counting. This was continued until 1969.
5. California State Department of Public Health—June 1964–December 1967
Intakes were estimated from house diets of hospitals in twenty different areas of the state. Seven-day-week food samples were collected once each two months and analyzed for ^{89}Sr , ^{90}Sr , ^{137}Cs , ^{141}Ce , ^{144}Ce , ^{95}Zn , and for stable potassium, sodium, strontium, and calcium.
6. Connecticut State Department of Health—March 1963–December 1967
The daily intake was estimated on a sample intended to represent the diet of an eighteen-year-old boy. Samples were collected monthly and analyzed for ^{89}Sr , ^{90}Sr , ^{137}Cs , and stable potassium.
7. Continuation under the Environmental Protection Agency and the Food and Drug Administration—1970–until gradually phased out

It will be noted that most of these programs terminated in the late 1960s because the levels of radioactivity were reaching amounts at or below the limits of sensitivity of all but very specialized methods. Nevertheless, the number of nuclear power plants being projected in the early 1970s spurred efforts for continuation of an analytical capability in case of a major accident. The Institutional Diet Program of the Bureau of Radiological Health of FDA was transferred to the Radiation Office of the EPA. This continued until 1973 when the occurrence of very low levels made the program impractical. This program involved all ten districts of the FDA plus analyses of some imported foods (seafish, shellfish, cheese, fresh fruit, canned fruit, tea, coffee, cocoa powder, and cashew nuts).

A typical picture for ^{90}Sr in the U.S. total diet is shown in table 12.16A, and the contributions of four major categories of food are shown in table 12.16B. The concentrations shown in table 12.16A are at the maximum observed and

TABLE 12.16A. Average Maximum ^{90}Sr Content of U.S. Total Diet (pc $\text{Sr}^{90}/\text{g Ca}$)

	"Wet" Area(a)	"Dry" Area(b)
	— Observed —	
1959	13-18	9
1960	11	4
1961	4-8	3-6
1962	8-13	4-8
1963 (Through March)	10	8
	— Predicted —	
1963	50	35
1964	30	20
1965	20	10

(a) The "wet" area includes all of the eastern and midwestern states west to about the Minnesota-Dakotas border, central Nebraska, the western third of Kansas and of Texas. It also includes the western half of Washington, Oregon, and most of northern California.

(b) The "dry" area includes the balance of those states listed above, plus all of Montana, Wyoming, Colorado, New Mexico, Utah, Arizona, Nevada, and most of Idaho.

Source: Modified slightly from FRC 1963.

TABLE 12.16B. Average Percent Contributions of Diet Categories

	Diet Weight ¹	Diet Calcium	Approximate Percent of Annual Strontium-90 Intake		
			N.Y.	Chicago	S.F. ²
Milk Products	33	61	51	39	37
Grain Products	14	15	16	26	24
Fruits and Vegetables	36	13	30	30	32
Others	17	11	3	5	7
	100	100	100	100	100

¹ The diet weights do not include water, coffee, tea and other nonmilk beverages.

² S.F. - San Francisco

Source: Modified slightly from FRC 1963.

predicted. Later figures (FRC 1964b) indicated that the predictions overestimated the maxima somewhat, not only for ⁹⁰Sr but for several other radioisotopes. The picture for several elements and for several components of the diet at this later time is shown in table 12.17. The strontium figures should be compared with table 12.16.

TABLE 12.17. Comparison of Predicted and Observed Levels of Radionuclides Deposited and in the U.S. Diet in 1963*

	"Wet"		"Dry"	
	Pred.	Obs.	Pred.	Obs.
Deposition (mc Sr ⁹⁰ /mi ²)				
Range	30-60		10-30	
Most Probable Value	50	45	20	25
Milk				
Sr ⁹⁰ (pc/liter)	30	25	10	15
Sr ⁸⁹ (pc/liter)	55	50	40	40
Cs ¹³⁷ (pc/liter)	140	125	—	85
Wheat (pc Sr ⁹⁰ /kg wheat)	250	220		
Flour (pc Sr ⁹⁰ /gm Ca)	40	40		
Total Diet (pc Sr ⁹⁰ /gm Ca)	50	30	35	10
New Bone (pc Sr ⁹⁰ /gm Ca)	12	7	9	2
Age 0-4 Bone (pc Sr ⁹⁰ /gm Ca)	5**	5	3**	2

* Except for bone, both predicted and observed values have been rounded to the nearest 5 units for purposes of comparison since this is considered to be more in keeping with the reliability of the estimates.

** Calculated from the observed strontium-90-calcium ratio in the diet.

Source: Reset from FRC 1964b.

Note: For definition of "wet" and "dry" see footnote to table 12.16A.

An important consideration arises in connection with the contribution of various diet categories. From table 12.16B, it is clear that milk contributes the most to strontium intake, especially in the "wet" areas because the average U.S. diet obtains much of its calcium from dairy products. It might be reasoned that switching to grains would reduce the burden of strontium in bone. This is not true because research we will review in more detail in chapters 13 and 15 has shown that there is more discrimination against strontium over calcium in the milk chain than in the cereal chain, so that the same original amount deposited will result in less deposition in bone from milk and dairy products. For these reasons, and despite the much lower consumption of dairy products in many other parts of the world, the strontium bone burden in the Orient, for example, was actually higher than in the United States and western Europe.

It must be realized that the figures given in the tables are subject to variations produced by differences in length of the growing season, agricultural practices, and, of course, the source term, fallout. Items such as fresh fruit and vegetables and fresh milk showed the most geographical variation, while staple items, including meat, were less variable, as were items that usually were composite in origin.

The picture in later years can be seen in results described by Simpson, Baratta, and Jelinek (1974 and 1977) and can be compared to the three ranges for action recommended by the FRC (see section VII). The intake via the total diet was, in 1974, 4.9 pCi/day of ^{137}Cs and 12.9 pCi/day of ^{90}Sr .

There were, of course, individual reports that interpreted the data from these many programs. Typical examples are a symposium held by the Federation of American Societies for Experimental Biology (FASEB 1963) and a review by Shleien (1970), based partly on surveillance data obtained at the Northeastern Radiological Health Laboratory of the Bureau of Radiological Health of the PHS. The maximum fraction of the FRC radiation protection guideline reported by Shleien was 17.8% due to ^{131}I in milk and the largest dose commitment that for ^{90}Sr in bone. It was approximately 10% of that from natural radiation sources.

b. Milk

The literature cited has copious detail on the radionuclide content of milk. We have already illustrated some of it.^(a) For our purposes here, the concentrations in the peak years, as shown in the FRC report (1964b), should be enough (figure 12.23).

It will be noted, as alluded to earlier, that ^{131}I is the most labile since it has the shortest biological and physical half-lives. Cesium-137 builds gradually over the entire period with a peak in mid-1963, and ^{90}Sr is more labile than ^{90}Sr , again because of its shorter half-life (physical in this case).

An interesting glimpse at some of the variations in geographical distribution, this time for ^{90}Sr in milk, is shown in figure 12.24. This represents, of course, a resultant of NTS and global fallout.

The influence of relative rainfall can be seen in the 40-pCi/l figures for parts of Arkansas and Louisiana that stand in contrast to stations not too far to the west but much drier. The 40-pCi/l line in North Dakota probably rests more on

(a) An especially complete summary can be found in the review of the PHS network findings given at the Hanford symposium on iodine (Dahl et al. 1963).

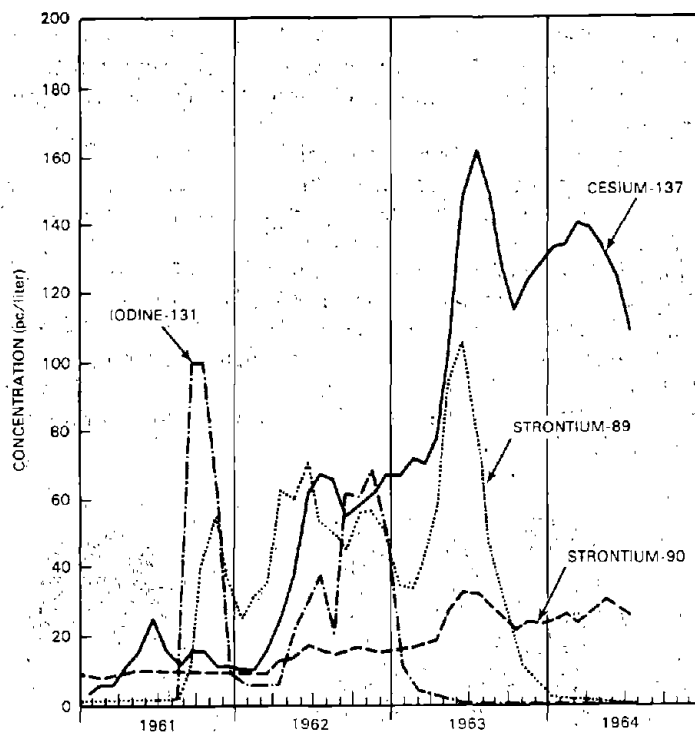


FIGURE 12.23. Average concentration of radionuclides in milk samples from Public Health Service pasteurized milk network (pc/l). (Redrawn from FRC 1964b.)

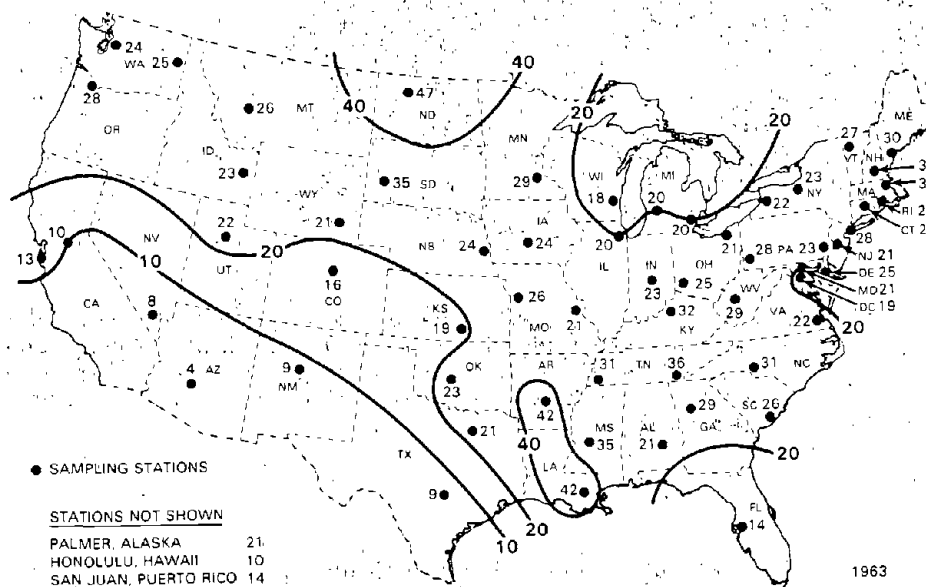


FIGURE 12.24. Strontium-90 concentrations in pasteurized milk. (Redrawn from FRC 1964b.)

transport to the northeast from NTS than on relative rainfall. Much laboratory and field research was built around these various milk sampling networks, and much was learned about the biokinetics of radionuclides in this segment of the ecosystem (chapter 15).

While we glibly quote summaries for milk and other food products, we should not forget that the analyses were far from simple, particularly in the years we are emphasizing. There is far too much natural radioactivity in substances like milk, e.g., from ^{40}K , to permit simple measurements of gross activity. The various isotopes had to be separated chemically and then their radioactivity measured. An example of the separation procedure in action for milk is shown in figure 12.25. This view shows a version of the procedure used at the Southwestern Radiological Health Laboratory in Las Vegas, Nevada. When it is realized that thousands of samples were analyzed by this or somewhat similar procedures, the enormous commitment of the biomedical community to these endeavors can be appreciated.



FIGURE 12.25. View of part of the procedure for analyzing milk for fission product radionuclides as carried out at the U.S. PHS Radiological Health Laboratory, Las Vegas, Nevada. Each radioisotope was measured separately insofar as possible. (Courtesy of Dr. Melvin Carter, Georgia Institute of Technology.)

As a footnote, we might add that the analysis for noble gases was especially laborious. Figure 12.26 shows one of the necessary steps in such a procedure at the same laboratory as shown above for milk. This analysis was probably not of milk, since there was little interest in the amounts of noble gases in milk.

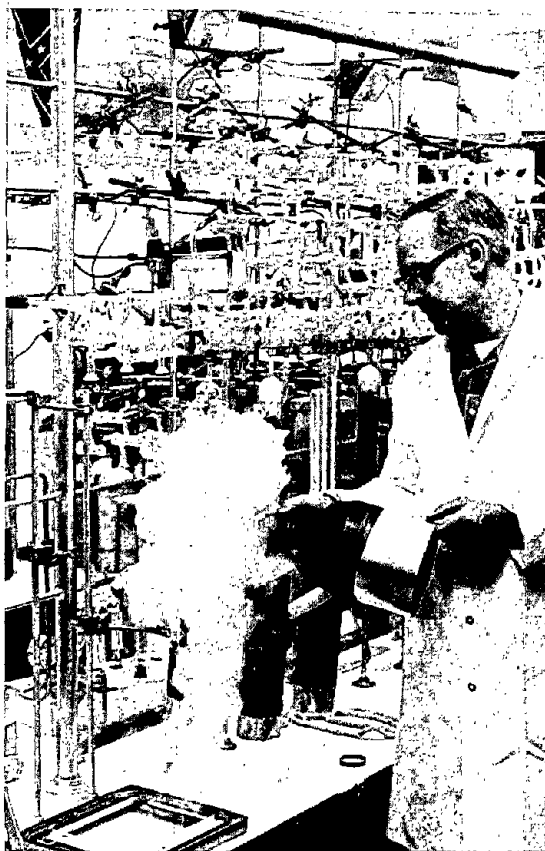


FIGURE 12.26. Part of the procedure for separating out noble gases from fallout fission products as carried out at the Southwestern Regional Radiological Health Laboratory of the U.S. PHS at Las Vegas, Nevada. (Courtesy of Dr. Melvin Carter, Georgia Institute of Technology, who is the operator in this picture.)

c. Wheat, Flour, and Cereals

Table 12.18 shows the progression of ^{90}Sr content of wheat and flour made therefrom over a five-year measured and a two-year predicted period from 1956 to 1965. Comparison to tables already shown points out that wheat contributed one of the highest concentrations of ^{90}Sr of all major foodstuffs at the peak of fallout activity.

The high radioactivity of wheat extended to other radionuclides as well. The reason for this seems to reside in a large contribution of foliar deposition and fewer discrimination factors between source and grain than in the milk pathway. (Note, however, the lower amounts in flour. This may represent partly processing and partly radioactive decay.) Contamination of all cereal grains turned out to be much more sensitive to the fallout rate between the time the grain headed out and its harvest than the other foodstuffs analyzed. It is less sensitive to either the cumulative amount in the soil or the total input from fallout. As a result, large variations may occur in the same crop grown in different areas or in crops grown in a given area at different times.

The high radionuclide content of wheat was responsible for at least one minor crisis in the administration of the fallout control program. The state health commissioner of Minnesota became alarmed at reports of rapidly rising radioactivity of wheat in the state and recommended widespread withholding

TABLE 12.18. Strontium-90 Content of Wheat and Flour in the U.S.* (picocuries per kilogram)

Year of Harvest	Average from 9-15 States Weighted for Production	
	Observed	
	Wheat	Flour
1959	50	10
1960	25	5
1961	25	10
1962	85	15
1963	220	40
	Predicted	
1964	140	20
1965	80	10

* Predicted and observed values have been rounded to the nearest 5 units for purposes of comparison since this is considered more in keeping with the reliability of the estimates.

Source: Reset from FRC 1964b.

of crops from the market. When this unilateral action by a state came to a head in Washington, there were objections based on the fact that, according to federal authorities, the RPGs of the FRC were designed for long-term exposure, not for short term. The ultimate result was the "Protective Action Guides," which we will review in section VII.

d. Water

Sampling of water was begun very early in the years of nuclear weapons testing.^(a) In 1955, radioactivity measurements were added to the National Water Quality Control Network. There were about fifty sampling locations. The work has been continued under the Federal Water Pollution Control Act as a cooperative project between federal, state, and local agencies. All of the major river basins in the United States were included.

The early results (see the Congressional hearings for 1959) showed very low activities in drinking water, partly because there are few entities in good drinking water to which radioisotopes can attach themselves or travel with. The work continued, however, largely as a routine operation of the PHS.

In early 1976, the EPA produced a large report on quality criteria for water. It did not include radionuclides, and it focused as much on aquatic life and recreational use of waters as on domestic uses. However, the EPA promulgated regulations for radioactivity in drinking water in July 1976 with a planned effectiveness date of June 24, 1977. The document describing the interim drinking water regulations (EPA 1976) for many types of contaminants gives a detailed discussion and maximum contaminant levels for both alpha- and beta-particle activities (see section VII).

(a) The sampling of water for content of naturally occurring radionuclides has been described in earlier chapters (e.g., 1 and 3).

Obviously, these recommendations from EPA were not developed with fallout phenomena particularly in mind. Nevertheless, it must be remarked that some of the proposed levels are now low enough that the maximal activities from fallout seen during the 1960s might equal or exceed the new recommendations. The criteria for water quality are currently in a state of flux, but in general the suggested levels are considerably lower than those used for many years, including the years of maximal fallout from weapons testing. (More later.)

e. Special Problems in Arctic Food Chains

Partly because of plans for a possible Plowshare event in Alaska (chapter 14), and partly because of general interest in the radioactivity distributed at northern latitudes from the Soviet tests in the early 1960s, considerable work was done in the Arctic and subarctic. It turned out that the cesium body burden of many residents of Alaska, northern Canada, Finland, and the northern USSR were from ten to one hundred times above the average. Peaks reached were 11,000 pCi/kg in central Canada; 11,200 pCi/kg in Finnish reindeer herders; 25,500 pCi/kg in Murmansk, USSR; and 9,100 pCi/kg in parts of Alaska.

Further, it turned out that the high figures were primarily in Eskimos, Inari (Finland), or others who ate large amounts of caribou or reindeer meat. The caribou and reindeer contained high concentrations of cesium in their flesh because of their diet of lichens. Lichens are long-lived, live on rocks, and provide a veritable sponge for the accumulation of fallout radionuclides. As we saw in the case of wheat, cesium seems particularly prone to remain on surfaces. Also, the lichens are radioresistant so that the accumulated radioactivity did not significantly reduce their viability. Thus, the combination of more than the usual accumulation of radioactivity and a short food chain, viz., lichen-caribou-(or reindeer)-man, resulted in the highest readings seen anywhere as a result of global fallout. Indeed, the amounts were sufficient to cause concern, and remedial action was considered. Fortunately, the levels began to recede before obvious harm had been done. We will have to wait out the question of whether or not long-term effects will appear. (More in chapter 21.)

Details regarding the work on global fallout in the Arctic and subarctic can be seen in UNSCEAR (1977, table 19, p. 145), Koranda and Martin from LLL (1971), Martin and Koranda (1971), Miettinen from Finland (1969), and Troitskaya et al. (1974) from the Soviet Union. (More in chapter 15.)

f. Discrimination Factors

The work on food, both field and laboratory, turned up biological phenomena that were in some respects the obverse of the concentration factors described in earlier sections of this chapter. In systems where the radionuclide of interest has analogues, and the two were followed together, as for example strontium/calcium and cesium/potassium, it frequently happened that the radioisotope passed through various steps in the food chain less readily than the stable analogue.^(a) At nearly all steps, we find for example that strontium is less readily absorbed, less readily deposited in bone, more readily excreted, etc., than its analogue, calcium. These differences were quantitated by the introduction of entities called discrimination factors. We will review them and some possible

(a) This is not because one member of the pair was radioactive and the other stable. The same phenomena were seen with stable strontium for example.

mechanisms when we consider laboratory research in chapter 13. They can result in very real differences between the amounts of some isotopes in fallout and the amounts eventuating in the tissues of man.

g. Protective Actions

Finally, in this brief consideration of food and water, we must emphasize the fact that those concerned with the evaluation of fallout worked out many types of protective actions that might be applied if needed. Obviously, they are more pertinent to the acute contaminating event than to the slow accumulation from global fallout. Yet, they could be activated if needed, even for worldwide fallout. In terms of dietary entities, the following can be mentioned:

1. shifting of cattle and other animals to stored feed;
2. impounding of contaminated feed to allow for radioactive decay;
3. diverting perishable commodities like milk to the production of processed foods;
4. removing radionuclides from food, e.g. milk;^(a)
5. reducing uptake of radionuclides as, for example, by the administration of stable iodine to flood the thyroid and reduce the uptake of radioiodines.^(b)

Even though some states have authorized stockpiling of stable iodine for potential distribution, there is still considerable hesitation in the medical community since the procedure has its own hazards. Recently, the California Medical Association drafted a position statement (CMA 1983) that suggests limited use if it is determined that the persons involved will receive a thyroid dose from radioiodines of over 25 rad. This, like other statements of position, has not yet been promulgated officially.

In general, the reason for developing guides for protective action has been as much to prevent unwarranted application of control measures, since they could frequently cause greater harm than the quantities of radionuclides present, as to control actions once the requisite level has been reached (see section VII).

D. Work in Other Countries

The international flavor of the enterprise concerned with global fallout has been obvious as we proceeded. Nevertheless, for the record, we should pause briefly to enumerate in one place the general nature of the research done and contributions made by organizations outside of the United States. The review will perforce be very cryptic.

The contributions came from individual countries and also from multinational organizations like the United Nations (UNSCEAR), the International Atomic Energy Agency (IAEA), and the International Radiation Protection Association (IRPA).

- (a) An elaborate system was set up by both industry and government to remove strontium from milk, for example, using ion exchange techniques; see U.S. Department of Health Education and Welfare pamphlet in the *Environmental Health Series* (DHEW 1967).
- (b) The pros and cons of the procedure of using stable iodine for prophylaxis have been aired almost from the beginning of consideration of environmental contamination by radionuclides. The thrust is more toward a potential nuclear power plant accident than fallout from weapons. Nevertheless, the *raison d'être* would be the same for cases of local fallout. We will glimpse the work briefly in chapter 19, where some of the literature will be cited. It is mostly clinical, not experimental.

The laboratories in the United Kingdom and Canada were on pretty much the same track as U.S. organizations. The important documents of the Medical Research Council have been cited already (MRC 1956, 1960). The table of contents of its 1960 report and its appendices are given as note 3 at the end of this chapter to provide not only an overview of the subject matter but a list of the investigators who contributed the several appendices.

Much of the U.K. work was experimental and will be considered in chapter 13. In the field situation, there were measurements of strontium in man (Loutit 1967 and 1969); measurements of environmental contamination from nuclear weapons (Russell and Bruce 1969; Bruce and Russell 1969); risk evaluation for protection of the public (Dolphin and Marley 1969); development of radiation protection standards for environmental contamination (Morley and Bryant 1969); research on transfer of ^{90}Sr through food chains to man (Bruce, Bartlett, and Russell 1967); and much work that appeared in later symposia of the IAEA and the IRPA. There was also an international symposium on strontium (Lenihan, Loutit, and Martin 1967).

From Canada, there was early work on the magnitude of the biological hazard from ^{90}Sr (Newcombe 1957, Chalk River) and ^{90}Sr fallout levels in Canada (Booth and Samuels 1969). The latter work, from the Canadian Department of National Health and Welfare in Ottawa, showed a marked effect of soil type on the amounts of ^{90}Sr in milk. There were low values in southern Ontario as compared to Quebec and New Brunswick (grey-brown podzolic with a natural high calcium content in the former and "true" podzolic with a lower natural calcium content in the latter). Other work from Canada can be identified through the index.

Work from France, which concerned food-chain contamination, has already been cited in part (Pellerin et al. 1967). Nearly all the IAEA symposia contain work from France.

There were occasional reports on the ^{90}Sr content of human bone in many countries, much of it quite recent work, e.g., Dehos and Kistner (1980) from West Germany.

The Japanese were busy too with, in addition to the extensive survey work described in connection with the Pacific tests, early reports on strontium and cesium (Izawa, Tsubota, and Nagai 1961.); fallout ^{90}Sr in beer (Shiraishi and Ichikawa 1970); (a) plutonium content of the soil of Nagasaki (Sakanoue and Tsuji 1971), which was well above background even twenty-four years after the bomb detonation; and also plutonium in human organs (Okabayashi 1979). These are just samples.

The extent and the depth of Soviet work can only be hinted at here. The USSR workers measured at least everything measured in the U.K. and U.S. work. They found higher body contents of fission product radionuclides than in U.S. or U.K. residents, especially in the far north for reasons discussed earlier. They also appear to have devoted much more attention to protection of their population. An excellent summary of USSR work to the mid-1960s can be found in the book by Petrov et al. (1966) already cited. The table of contents of his book is shown as note 4 at the end of this chapter.

(a) It was not high enough to cause concern but showed that the contamination was entering by way of the raw materials used for making the beer.

The Soviet volume is very complete with nomograms for determining external dose from fallout, re-entry times permissible after different contaminating events, additional radiation dosage that can be allowed at various times after a single justified-risk dose, etc. It also has much detail on the doses from fission products taken internally and descriptions of applicable field instrumentation. Although considerably shorter, this volume may in some areas be more complete than the U.S. volume, *The Effects of Nuclear Weapons*, already cited.

Further citations to work done abroad as well as in U.S. laboratories can be found in a bibliography of the world's literature up to 1961 prepared for the U.S. AEC by Bost, Vorees, and Smelcer (1961).

VII. Standards For Fallout^(a)

Throughout the discussions in this chapter, we have indicated how the amounts of radionuclides found in the biosphere, including humans, might be related to certain criteria of possible effectiveness. These criteria were developed, sometimes directly sometimes rather complexly, from recommendations of bodies such as the NCRP, the International Commission on Radiological Protection (ICRP), the IAEA, the National Academy of Sciences, and via regulations developed by various federal and state authorities, including for the test sites, the military (Hacker undated). Much computational research went into these efforts, although not much laboratory research could be brought to bear except for metabolic cycles, transfer coefficients, and the like. A large segment of the biomedical community was involved, in one way or another.

A general though brief discussion of the cognizant organizations and the general processes of setting standards for exposure to radionuclides is given in chapter 16. There were, nevertheless, facets peculiar to environmental contamination that are better discussed here as part of these chapters on environmental aspects of radionuclide releases. They apply, of course, as much to contamination from general nuclear activities, including nuclear reactors, as to fallout from nuclear weapons tests, but since they grew largely around the problems of local, regional, and global fallout, they are appropriately discussed here.

(a) Note added in proof: In July 1986, S. C. Black and G. D. Potter at the EPA Laboratory in Las Vegas published a historical perspective of selected health and safety aspects of nuclear weapons testing (*Health Physics* 51:17-33). This is a compact, authoritative, and carefully researched summary of much of the material reviewed in this chapter, particularly that pertinent to standards and offsite exposures. It provides updates to some of the sections and adds specific references to AEC and PHS reports that were either not available or not known to this author at the time of writing. These include AEC reports on the continental tests, very specific information on exposure standards for NTS, and work of the PHS in measuring iodine burdens in people following an event labeled "Palanquin" (a Plowshare event) and one labeled "Pin Stripe." There is much more discussion of the role of instrument development in developing and applying standards for fallout than was possible in this chapter. The author's point, consistent with the thrust of this chapter, to "serious over-sight affecting human exposure, namely, that of not recognizing the relative information of all potential transport/dosimetric pathways for risk assessment." Yet, the picture drawn is primarily one of conscientious application of the knowledge then available.

A. Early Activities

The several organizations concerned with testing could not wait for development and promulgation of formal special standards. Ad hoc levels were chosen for activities such as "Operation Crossroads" and those at NTS in the early 1950s. The standards for radiation protection set by the AEC for the 1953 series at NTS as developed by a special committee were as follows:

1. The external dose to non-participating inhabitants of radiation from gamma rays shall not exceed the accepted international permissible dose level of 300 mR/week, which may be integrated over a maximum of ten weeks.*
2. At a point of human habitation, the activity of radioactive particles in the atmosphere, averaged over a period of 24 hours, shall be limited to 100 microcuries per cubic meter of air (corresponding approximately to a ground level gamma intensity of 30 mR per hour).
3. The 24-hour average radioactivity per cubic meter of air, due to suspended particles having diameters in the range of 0 microns to 5.0 microns, shall not exceed 1/100th of the above; nor is it desirable that any individual particle in this size range have an activity greater than 10^{-2} microcuries calculated 4 hours after the blast.

*Subsequently modified to allow integration over the duration of the test series which in 1953 was 13 weeks or 3.9 R.
(Johnson and Carter 1984, p. 1270).

It will be noted that only gross activity from radionuclides was stated—partly because the instrumentation could not distinguish among isotopes except crudely. The resemblance of these to NCRP and ICRP recommendations and the Code of Federal Regulations for occupational exposure is more than fortuitous.

Some of the individual laboratories felt a need to devise criteria for specific radionuclides in the environment, much as they had done in the MED for occupational exposure. A general effort aimed at maximum allowable concentrations of fission products in the air was carried out by the Radiological Division of the U.S. Army Chemical Corps (Harvey 1952).

During the 1957 U.S. Congressional hearings, there were many discussions that involved, either formally or informally, questions of standards for exposure of the population to fallout (see, for example, Dunning 1957b). These took two forms: (1) what levels were permissible, and (2) discussions of how long testing could continue at the then-current rate or even how much the rate could be increased before the amounts of fallout radionuclides in the biosphere and in humans would reach unacceptable levels. We will address the permissible levels and their evaluation first.

In earlier sections, we described the Sunshine Unit as $1 \mu\text{Ci } ^{90}\text{Sr/gCa}$ and the occupational limit then accepted as $1,000 \mu\text{Ci/gCa}$. Also, we saw that those concerned with the Sunshine Project suggested a population dose of one-tenth of the occupational,^(a) or $100 \mu\text{Ci/gCa}$ (100 Sunshine Units). This idea had a certain amount of informal backing in organizations like the NCRP, but neither the NCRP nor any of the other recommending bodies issued a formal declaration of policy on population exposures at this early time. The early report of the National Academy indicated disagreement among the committee members. As quoted by Brues at the 1959 hearings (p. 1321), the report indicated:

(a) The philosophy of this relation and others is discussed in chapter 16.

First responses to the question (i.e., permissible dosage to large populations) ranged all the way from the permissible industrial level down to no radiation at all. . . . The uncertainty . . . stems from our ignorance as to whether or not there is a true threshold for such late effects as malignant tumors and the degree of variation in response of equally exposed individuals.

This was before the radiation protection fraternity had decided that "for prudence" a linear no-threshold response should be assumed to hold. The question of the presence or absence of a threshold permeated all of the discussions in those days.

Furthermore, people quite understandably got hung up on the numbers. Assuming linearity, the radiation from fallout could be calculated to produce two extra cases of leukemia in the combined populations of Baltimore and Washington, i.e., 202 per year instead of 200, in a population of three million; 100 extra cases per year in Japan, i.e., 10,100 instead of 10,000 in a population of one hundred million; or 1,500 extra deaths from leukemia per year in the world population. Since both leukemia and bone cancer were assumed to be produced by the deposition of ^{90}Sr , it was easier to lump the statistics for both in estimating long-term effects. On this basis, and assuming a linear no-threshold dose-response relationship, a total of 50,000 total cases was calculated as attributable to fallout over a thirty-year period in the world population (Selove, in U.S. Congress 1957, p. 1292). It was also calculated that 12,000 extra deaths from leukemia and bone cancer would potentially occur in the U.S. population over the thirty-year period (U.S. Congress 1957, p. 1296). Like all such calculations, these show the effect of multiplying even a quite low incidence rate by a very large population.

We are still struggling with this problem of the numbers not only for radiation-induced changes but any other effects whose dose-response curve is assumed to be linear with no threshold. The percentages may seem minuscule until the numbers are multiplied by the population of the world. We will always face this dilemma, especially in the balancing of risks and benefits. Yet, only by such balancing will we attain solutions.

Another factor that entered the early deliberations on standards for fallout was the "worry level." It is now common practice to report, even require action, at levels only a fraction of the ones chosen as "permissible" and to have all operations at levels as low as reasonably achievable (ALARA). William F. Neuman in his testimony at the same hearings (p. 1319) expressed the view that the British report (MRC 1956) had adopted a figure of 10 Sunshine Units as a "worry dose" at which the rate of testing and other factors should be re-examined carefully before the inexorable climb of radionuclide content of the body progressed beyond the permissible level.^(a) The general idea of a worry dose received support from others, e.g., Langham at the same hearings and in other discussions.

(a) The statement in the MRC report is ". . . we believe that immediate consideration would be required if the concentration of radioactive strontium in bone showed signs of rising greatly beyond that corresponding to one hundredth of the maximum permissible occupational level." Since the occupational level was 1,000 Sunshine Units, the "worry level" became 10 S.U. The 1960 NAS-NRC report does not use quite the same terminology and puts the "warning level" at one one-hundredth of the occupational and one-tenth of the population level.

These considerations were not limited, of course, to strontium. Levels were similarly set for other important radionuclides. The processes were similar for all, except that the bone seekers were related to radium, the soft-tissue seekers to the permissible doses for external low-LET radiation.

The second facet of the discussions, i.e., how long and at what rate could testing continue before the MPC was reached or exceeded, brought in the results of laboratory as well as field research. First there had to be good data for the rate of fallout, its accumulation with time, the inventory still to come, and the passage from soil or air to the tissues of humans. We have already seen examples of how most of these entities were estimated. For the final step, we can turn again to the 1957 hearings. An example is given below.

Neuman was unhappy with using ^{90}Sr as produced in the past for predictions because "these data are inextricably bound to past conditions, testing rates, types of weapons exploded, and so forth." Instead he developed a model using measured behavior of *natural* strontium compared to *natural* calcium to see to what degree strontium was a "counterfeit" for calcium. As we saw earlier, it was not an exact match. His model proposed that the strontium/calcium ratio in passing through each organ or process in the chain from ingestion to deposition in human fetus or mother's milk or cow's milk was reduced by one-half. With four major processes—gut absorption, urinary excretion, blood to placenta or mammary gland, and placenta to fetus or to milk—the overall change in ratio or the overall discrimination factor was eight.

To go further, it was assumed that at equilibrium the amount of ^{90}Sr that can be produced will be equal to that which decays in any given year, or 2.5% per year due to the relatively long half-life of ^{90}Sr . The rest follows. Introducing the discrimination factor and corrections for stratospheric hold-up time, the non-uniformity of fallout, and the nonuniformity of population intake and response, it was possible to calculate a tolerable ground-level concentration, and from it a maximum test rate (see p. 715 of the cited hearings for details).

Thus, using an MPC in bone and figures for the amounts of ^{90}Sr produced per megaton of fission, a limiting testing rate could be calculated. Using an MPC of 100 Sunshine Units, the limiting equilibrium test rate came out as 4.4 MT equivalent of fission products injected into the stratosphere annually. Using an MPC of 50 Sunshine Units, the limiting rate was, of course, 2.2 MT equivalent per year.

Other calculations were made using somewhat different quantities for the parameters and radiostrontium rather than natural strontium. Yet, the eventuating equilibrium rates were not widely different considering the many assumptions and uncertainties involved.^(a)

At the time of these early hearings, 2.2 or even 4.4 MT of fission per year seemed safely ahead of the actual testing rate. Indeed, some of those interested pointed out that it would take decades just to reach the equilibrium value! This soon changed with the marked increase in megaton equivalents associated with hydrogen bomb tests. The temporary test ban near the end of the decade of the fifties was welcomed by all biologists as one way to check out these myriad calculations before processes of serious biological harm could be unwittingly initiated.

(a) Perhaps this figure for maximum allowable concentration was firmer than many of the others, for it was based on the well-established MPC of ^{226}Ra in bone and the toxicity of strontium relative to it determined directly in animal experiments.

B. Establishment of Population Exposure Standards

The above standards closely resemble those for occupational exposure. There is little doubt that the exigencies of the fallout problem, along with the possibilities for environmental contamination from sources such as nuclear reactors, stimulated the recommending bodies to work in some depth on the formulation of limits for population exposure. The influx of information on genetic effects would have seen to this if nothing else had done so. The AEC's standards as promulgated in the Code of Federal Regulations included figures for population exposure for all isotopes (table II of Appendix B of Code 10 CFR 20 1972). However, except for iodine, a case we have already discussed, they were simply scaled down from the occupational levels by a factor of ten.

Publication 7 of the ICRP (ICRP 1965a) introduced the concepts of critical nuclides, critical exposure pathways, and critical population groups. In each case, these represented the entity most likely to give or to receive the highest dose or to involve the greatest hazard (more in later chapters). This greatly simplified the setting of standards for the public around sites of environmental contamination and provided many economies in the conduct of environmental monitoring. These concepts have continued in use over the decades since.

A very helpful analysis of how dose limits for members of the public differ from dose limits for occupational exposure is given by Sowby (1969) from the United Kingdom. He points out the very real problems of actually checking the magnitude of the dose received by individuals in the population.

Publication 9 of the ICRP (1965b) expanded on the exposure of populations, especially the genetic dose limit. As we will see in chapter 16, there was a period when not only the ICRP but the American counterparts such as NCRP and the National Academy, and also the United Nations Scientific Committee issued separate limits for genetic and for somatic effects. However, the genetic limit was couched in terms that permitted more planning for avoidance than for assessment or remedial action. The general levels for population exposure were still about one-tenth of the occupational.

By far the most comprehensive approach to population standards during the years of most concern about fallout was that of the FRC. (For its organization and development, see chapter 16.) In its first report (FRC 1960), it introduced the term "Radiation Protection Guide" to emphasize the philosophy that there can be no single permissible or acceptable level of exposure without regard for the reasons for permitting the exposure. It suggested population exposure guides of 0.5 rem per year to the whole body for the individual (i.e., one-tenth of the normal occupational guide) and 5 rem in thirty years to the gonads for the population average. The latter was based on potential genetic changes. It was identical to the 0.17 rem per year developed from the assumption that the average dose to even a small population group should be lower than that allowed an individual. A factor of three potential difference in sensitivity was assumed, and the figure thus became $0.5/3$ or 0.17 rem/year. The genetic dose was theoretically to be applied to relatively large population groups. It would thus be particularly applicable to global fallout and isotopes like ^{14}C that might deliver a genetically significant dose.

The second FRC report (FRC 1961) introduced the idea of ranges for the RPG for both occupational and population exposure. Range I encompassed intakes that would not be expected to result in any appreciable number of individuals in a population reaching a "large fraction" of the RPG. Range II represented

intakes that would be expected to result in average exposures to population groups that might approach but not exceed the RPG. Range III represented intakes that would be expected to result in exposures exceeding the RPG. Recommended degrees of control ranged from routine surveillance through active surveillance to consideration of positive control measures for the three ranges, respectively.

Each radionuclide of high importance to fallout problems was examined in detail, and figures were derived specifically for that isotope; quite a different procedure from the simple application of a scaling factor. The report also discussed concentration values related to the applicable RPGs but warned against indiscriminate application without due regard to the environmental medium contributing the intake, i.e., food, water, air, or combinations thereof.

The figures given in the second report are:

	¹³¹ I	⁸⁹ Sr
Range I.	0-10 $\mu\text{Ci/day}$	0-200 $\mu\text{Ci/day}$
Range II.	10-100 $\mu\text{Ci/day}$	200-2,000 $\mu\text{Ci/day}$
Range III.	100-1000 $\mu\text{Ci/day}$	2,000-20,000 $\mu\text{Ci/day}$
	⁹⁰ Sr	²²⁶ Ra ^(a)
Range I.	0-20 $\mu\text{Ci/day}$	0-2 $\mu\text{g}/\text{day}$
Range II.	20-200 $\mu\text{Ci/day}$	2-20 $\mu\text{g}/\text{day}$
Range III.	200-2,000 $\mu\text{Ci/day}$	20-200 $\mu\text{g}/\text{day}$

It will be noted that Range II is about equivalent to the 10 CFR 20, NCRP, and ICRP numbers, but is not necessarily a factor of ten below the occupational limit in each case, particularly since it is a range.

These numbers were, of course, not available yet at the time of some of the most intensive discussions of limits for fallout described in the previous section. They were, however, available for the deliberations of the 1960s.

Although the figures for the RPGs for population exposure were useful guides, they assumed long-term intakes. As described in the previous section, application of the RPGs to short-term exposures, such as an acute contaminating incident or the passage of a fallout cloud, was frowned upon in official circles. Yet, those responsible for any needed action complained that they had no guidance other than that for long-term exposure. This stimulated the FRC to devise a new set of guides called "Protective Action Guides," which were developed in reports number 5 and 7 (FRC 1964a, 1965).^(b) There were special advisory panels on environmental factors and dosimetry and a special report from an advisory committee of the National Academy of Sciences-National Research Council (NAS-NRC 1964) on the implications to man of irradiation by internally deposited ⁸⁹Sr, ⁹⁰Sr, and ¹³⁷Cs. The composition of the FRC, the NAS-NRC advisory committee, and the ad hoc panels are given as note 5 at the end of this chapter.

A Protective Action Guide (PAG) is the *projected* absorbed dose to *individuals in the general population* that warrants protective action following a contaminating event. The FRC considered both the acute localized contaminating event and worldwide contamination from stratospheric fallout. They considered

(a) Not of interest to situations involving fallout from weapons tests.

(b) Reports number 2, 3, and 4 concerned estimation and evaluation of fallout but not radiation protection standards (FRC 1961, 1962, 1963).

isotopes in three categories: I.—transmission limited to the pasture-cow-milk-man pathway, II.—transmission through other dietary pathways, and III.—long-term transmission through soils to plants in the years following a contaminating event.

The PAGs developed by the FRC can be summarized as follows:

Iodine-131 and the thyroid—a projected dose of 30 rad to the thyroid of individuals in the general population. It is assumed that this condition will be countered effectively if the average projected dose to a suitable sample of the population does not exceed 10 rad (FRC 1964a). A table is given for calculating thyroid dose from different estimated intakes. Since ¹³¹I has short radiological and biological half-times, these recommendations have significance only for the relatively acute contaminating event.

Strontium-89, strontium-90, and cesium-137—for a category-I transmission, a mean dose of 10 rad in the first year to the bone marrow or whole body of individuals in the general population, provided that the total dose does not exceed 15 rad.

For category-II pathways, a mean dose of 5 rad in the first year to the bone marrow or whole body of individuals in the general population.

Operationally, it was suggested that the PAG would be met effectively if the average dose to a suitable sample of the population is maintained at or below one-third the PAG, i.e., 3 rad for category I and 2 rad for category II.

No PAG was recommended for category III.

Worldwide Contamination from Stratospheric Fallout—The FRC did not recommend PAGs for this situation. Their reasoning follows:

Reduction in transmission of radionuclides to man under worldwide fallout conditions could only be achieved by long-term changes in (1) agricultural practices, (2) food processing practices, or (3) basic dietary habits. Consideration of such basic economic and social changes is not warranted when annual doses from environmental contamination are comparable to the numerical value of the annual dose recommended for the RGC. It has not been possible to visualize circumstances in which the balancing of the risk of radiation against the undesirable consequences of the protective measures on social, economic, and political institutions can be reduced in advance to numerical guides for mandatory action under these circumstances.

On the basis of this information on stratospheric fallout the Council concluded that the health risk from radioactivity in food over the next several years would be too small to justify protective actions to limit the intake of radionuclides either by diet modifications or by altering the normal distribution and use of food, particularly milk and dairy products.

In view of these considerations it is recommended that:

Surveillance of the radionuclide content in food products contaminated with worldwide fallout be continued at levels appropriate to the situation.

Surveillance and research programs examining the special ecological situations in the arctic region continue until future trends can be predicted with greater confidence.

Nationwide programs to reduce potential exposure of the population from gradually increasing levels of environmental contamination, such as that associated with worldwide fallout, are not necessary now nor for future levels of fallout from past testing. (Quoted with slight organizational modifications from FRC 1965.)

The promulgation of the PAGs caused both resentment and misunderstanding in parts of the biomedical community. It was argued that "radiation is radiation," and it should not matter whether the source was fallout, a nuclear installation,

or any other. However, after some careful explaining, the point was accepted, viz., it was not so much the source as the time course of the exposure that made the difference.

Quite clearly, the FRC's actions were more helpful quantitatively to evaluation of local fallout and events such as those around the test sites than to global fallout.

The setting of exposure standards for the population has not ceased in the intervening years, but it has, of course, changed in emphasis away from fallout problems per se.

In its 1971 basic radiation protection criteria report, the NCRP set dose limits for the public or occasionally exposed individuals at 0.5 rem in any one year and population dose limits at 0.17 rem average per year for either genetic or somatic effects (NCRP 1971). The NCRP did not develop population dose limits for individual radionuclides. The AEC and its successor for regulation, the Nuclear Regulatory Commission, stuck assiduously to the limits for radionuclides shown in Appendix B table II of the Code of Federal Regulations, Part 20, except for the modifications in Appendix I already described. This may change in the near future. (P.S., still waiting in 1987.)

In 1979, the ICRP adopted a report on the assessment of doses to man from radionuclide releases into the environment (ICRP 1979). This considered both planned and unplanned releases and is full of modeling for dose predictions and the use of dose predictions in decision making. The report is essentially a supplement to and expansion of Publication 7 already cited. Dose commitment in the sense first used by UNSCEAR to apply to the consequences of fallout was applied generously. The modeling utilizes two quite different methods, the concentration factor method and the systems analysis method. Since no new numerical guidance is introduced in this report, we will not discuss it further now except to recommend it to the reader interested in examining current philosophy and methodology. It is understood that the ICRP is now working on a comprehensive analysis of population exposure standards.

In the United States, the FDA Administration prepared guidance concerning radioactive contamination of human food and animal feeds (*Federal Register* 1978). This guidance proposed a "preventive" PAG applicable to situations where the protective actions would cause minimal impact on the food supply and an "emergency" PAG applicable to situations where the actions could have considerable impact on the food supply but were justified by the magnitude of the projected health hazards. The levels proposed were:

Preventive Guides(a)	¹³¹ I		¹³⁷ Cs		⁹⁰ Sr		⁸⁹ Sr	
Initial Deposition (μCi/m²)	0.14		1.7		0.34		6	
Total Intake (μCi)	0.09		7		0.2		2.6	
Emergency Guides	Infant/Adult ¹³¹ I		Infant/Adult ¹³⁷ Cs		Infant/Adult ⁹⁰ Sr		Infant/Adult ⁸⁹ Sr	
Initial Deposition (μCi/m²)	1.4	18	17	65	3.4	25	60	3,000
Total Intake (μCi)	0.9	10	70	110	2	12	26	1,000

(a) Infant as critical segment of the population.

These guides were derived from and are closely related to those prepared fourteen years earlier by the FRC and were planned as replacements for them.

Doses associated with these, including addition of a new category of "Alert," are given below (NRC 1977):

PAG	Alert (Average Dose)	Preventive (Dose Commitment)	Emergency (Dose Commitment)
Thyroid	50 mrem/yr	3,000 mrem	30,000 mrem
Bone Marrow or Whole Body	17 mrem/yr	1,000 mrem	10,000 mrem

The resemblance of these figures to others we have been considering are not immediately obvious. The supporting documentation presents the arguments and derivations.

The recommendations of the Bureau of Radiological Health (BRH) were considered not sufficiently conservative by some, e.g., Swick and Morgan (1980). Shleien of BRH responded to the criticisms by pointing out that the PAG was a *projected* dose commitment rather than one that is actually reached and also that certain numbers had not been quoted or used correctly (Shleien 1981a). There is now a fairly consistent cadre of individuals who feel that all of the present standards for population exposure are too high, with the possible exception of the new EPA guidelines that are very low indeed. The current status of these proposals from FDA is not known to this author.

Recently, the CRC Press has developed a *Handbook of Environmental Radiation*. A chapter in it by Denham and Waite (1982) considers "Action Guides and Countermeasures." Considerable space is devoted to Emergency Defense Levels for many radionuclides important in fallout. Also, it summarizes international codes and criteria for the transuranic elements. The data are assembled from sources quoted earlier in this chapter and in chapters 11 and 16.

The new EPA guidelines are still in preparation except for a few radioactive substances. We should mention that, in addition to the guidelines being prepared for environmental components, especially water, the EPA developed in the mid-1970s an entity known as "Environmental Dose Commitment," which was aimed more at contamination from nuclear reactors than from fallout. It was an extension and refinement of the average dose commitment developed in the 1969 UNSCEAR report largely around the problems of fallout. While the UNSCEAR formulation was based on an infinite time integral of the average dose rate in a population, the EPA took into account expected changes in population size and computed a collective dose rather than an average dose. The EPA viewed their method as supplying a better assessment of the total impact of, for example, the nuclear power industry. These matters are discussed by Richardson (1975), who quotes a very similar projection system developed by Beninson (1974).

VIII. Dilemmas, Problems, and Progress

A. General Comment

There can be no doubt in the mind of anyone reading this chapter that fallout from nuclear weapons tests brought a shower of dilemmas and problems upon the scientific community and society in general. Most of the dilemmas and

many of the problems were as much political and moral as scientific and technical. It is not appropriate here to expound in any detail on the former. Yet, in some instances scientific and technical aspects were so intimately intertwined with the political and moral questions that they require comment, even here.

1. Should We Have tested?

A persistent dilemma for the biosociopolitical community and for society in general has been this one. In a sense, the question was not so much a dilemma for individual decision makers as a collective dilemma with the weapons designers and those responsible for national security on one side and much of the biomedical community on the other. The second volume of the history of the AEC by Hewlett and Duncan (1969) gives the picture of the milieu in which the AEC had to work in the period 1947 to 1952. A more personal account is contained in the autobiography written by Lewis Strauss, chairman of the AEC during many of the critical years of weapons testing. The book is entitled *Men and Decisions* (Strauss 1962).^(a) Chapter XIX, "Nuclear Tests, Fall-out, and World Opinion" concentrates on the testing dilemma as seen by one who had to make decisions on both sides. Strauss begins his chapter as follows:

This is a chapter about a subject which many people find repulsive. It offends reason to think that, at this point in human development, experience should not be overwhelmingly convincing that war is the most witless of human enterprises. It is a fact of life, however, that experience frequently fails to convince.
(Strauss 1962, p. 404)

After considerable exposition of the AEC's involvement with nuclear weapons development, interaction with the military, and some description of the Pacific tests and the numerous reports on all aspects, including biological effects, Strauss epitomizes the position of the AEC regarding the Pacific thermonuclear tests as follows:

As soon as the scores of scientific reports had been submitted and studied, a comprehensive report was issued the following February under the caption "A Report on the Effects of High Yield Nuclear Explosions." In an introduction, attention was called to the fact that "If we had not conducted the full-scale thermonuclear tests in question, we would have been in ignorance of the extent of the effects of radioactive fall-out and, therefore, we would have been much more vulnerable to the dangers from fall-out in the event an enemy should resort to radiological warfare against us. . . ." Also, "In the event of war involving the use of atomic weapons, the fall-out from large nuclear bombs exploded on or near the surface of the earth would create serious hazards to civilian populations in large areas outside the target zones. The Atomic Energy Commission hopes that these dangers will never be experienced by mankind. However, until the possibility of an atomic attack against us is eliminated by a workable international plan for general disarmament, the study and evaluation of the effects of weapons which might be used against us and the improvement of our means of self-defense are a paramount duty of our government."
(Strauss 1962, p. 412)

(a) The author is indebted to Dr. H. David Bruner, Bonita Springs, Florida, formerly of the AEC, ERDA, and DOE staff for providing me with a copy of this book and much other pertinent literature.

Biomedical problems receive increased emphasis on each succeeding page, but Strauss returns to his original theme near the end of the chapter, "the real danger to the human race is not the continuance of weapons tests. The real danger is nuclear war" (Strauss 1962, p. 424).

Given those alternatives, the biomedical community saw no dilemma either. What seemed to be hardest for the biomedical community to get across was its concern for the large gaps in our biological knowledge. The admonition to hold back as much as possible while ongoing research on the long-term effects of fallout, indeed of ionizing radiation from any source at low levels, could gather the critically needed new data did not mean that the biomedical community was against national security. However, there was reason for emphasis on keeping the testing rate low and for the strong presentations to the military to do the least possible testing and finally to move all testing underground.

The long-term experiments at Argonne, Davis, Hanford, Los Alamos, Lovelace, Rochester, and Utah, etc., were started partly, though not exclusively, to approach these questions. It is a commentary on the time needed to do thorough biological work on large animals that many of these experiments are just now coming to satisfactorily documented conclusions—ones that can help support estimates of risk. The earlier scientific dilemma would have been less acute had we had these firm data, but we are not home free even now.

2. Risk Versus Benefit

As noted earlier, and to be emphasized in later chapters, the view grew during the years of the fallout controversy, though not exclusively because of it, that the radiation dose-response relationship had to be regarded as linear with no threshold. Thus it followed that any extra radiation produced extra risk. The corollary was that there should be no radiation exposure unless there was a concomitant benefit. The review in this chapter should make it clear that fallout confers no direct health benefits. Any benefits had to be in other quarters.

The weapons-testing situation did not facilitate specific descriptions of benefits. The generalization that national security required weapons testing was vague indeed compared to the reasonably obvious benefit of an x ray for diagnosis. Furthermore, in the early days, the biological risk could not be spelled out with any precision. We thus had two relative unknowns—the details of benefits to the nation's security from improved weapons design and the details of the biological risk. The former were locked up by classification (they might not have been understood anyway); the latter were in dire need of quantification. No wonder there was agitation and controversy!

Much has been said about the withholding of important information during the testing years. This clouded the balance of risks and benefits. This author is in no position to comment except to state that in over one hundred interviews in preparation for this book (see Appendix A), lack of knowledge was decried much more than withholding of knowledge beyond the needs of national security. It was the public relations aspects of the operation that drew the most criticism.

In contemplating the two aspects of the dilemma of testing, one wonders if there was ever or ever could be any one individual, even the President of the United States, even the chairman of the AEC, who was fully cognizant of both sides of the equation, i.e., a person who knew in *equal depth* both the true value of the information obtained from testing and the true dimensions, small or large, of the biological risks being countenanced. It seems most unlikely. The

result was a need for consultation and weighing of the evidence given by experts with very disparate backgrounds. And behind it all was the fact that we did not know the answers to the biological questions. We still do not, although we have made much headway. Before we indulge in unbridled criticism of our fellow citizens, we should remember that our largest problem was and is, ignorance. Nature gives up her secrets with great reluctance.

B. Hidden Doses

At several points in this chapter, we have pointed out that the second part of the dose from fallout, the possible long-term effects from ingestion or inhalation of radionuclides in contrast to the external radiation dose, had been either neglected or measured rather superficially. This was true even for possible short-term effects, except for Operation Crossroads, the Marshallese, and some other events in the Pacific. It took the iodine scare to bring the possible role of food-chain contamination or direct contamination of humans from radionuclides of continental or global origin into proper focus. We also pointed out the accepted maxim at the test sites that maintenance of the external dose below limits would automatically protect against internal dose from inhalation or ingestion. We know this was correct only for close-in, relatively fresh fallout and even then not fully correct. It was less correct still for longer-term exposure via environmental contamination. Because of these facts, we could say that there was something missing from the accounts, and that this may have contributed in some degree to the ultimate risk.

John Gofman, whose work and opinions we have met in other chapters and whose treatise on low-level radiation effects we have already cited (Gofman 1981),^(a) attached the colorful term "hidden dose" to these phenomena. He cited specifically (1) additional internal dose possibly received by the men involved in the "Smoky" and related incidents, (2) a possible contribution of a dose from fallout to the dose-response relationships and the dosimetry of the Japanese at Hiroshima and Nagasaki, and (3) unexplained incidence of leukemia in individuals who entered Nagasaki soon after the bombing.

The first instance is essentially identical to what we described in section V, except that Gofman applied the reasoning to the analysis of Caldwell, Kelley, and Heath (1980) and quantitated the "hidden dose" by comparison of the leukemia incidence in the "Smoky" cohorts to that in the Hiroshima-Nagasaki survivors. The rate was much higher for the men at "Smoky." Either there was some additional dose that was not counted, or the two groups responded to grossly different extents on a per-rem basis. The former is a more logical explanation.

Despite the obvious importance of the "hidden dose," Gofman does not try to use the incidence figures for the soldiers for any of his predictive calculations "since the true dose received by these soldiers is unknown" (Gofman 1981, p. 684).

The second use that Gofman makes of "hidden dose" concerns entirely external radiation and has, therefore, not been mentioned before in these pages. Since the dosimetry for the Japanese is now in a state of flux, we must await further analysis. An important point is the finding of increased chromosome

(a) The book is largely a computational approach to the problems of radiation standards and basic radiobiology at low doses but provides also many unique descriptions of events and situations.

aberrations in individuals well beyond the range of the prompt external radiation. Was there a fallout cloud that went undetected? Gofman postulates that there was and that there were higher doses in the area. Japanese investigators Sasaki and Miyata (1968) found persistent chromosome aberrations in individuals checked out as having been beyond 2.4 km from the hypocenter yet close enough to have been in a fallout cloud if there had been one.^(a) This postulate has many implications for all of the low-dose regions of the Japanese dosimetry, in this case, an increment of external dose contributed by the possible fallout cloud.

At the beginning of this chapter, we indicated that no published measurements were available for fallout from Hiroshima-Nagasaki except for some soil-sample data near Nagasaki (Nishiyama district) taken long after the event and the finding still more recently of residual plutonium near Nagasaki. There is no way we can go back and reconstruct fallout maps as was possible around NTS. The only evidence we have is the biological indicator, chromosome aberrations, and the residual fallout in soil from that same Nishiyama district of Nagasaki (Okajima et al. 1978).

The third way in which Gofman utilizes the possible role of a "hidden dose" is based upon work by Sztanyik (1978), which he quotes. This concerns unexplained radiation effects in early entrants to that same Nishiyama district of Nagasaki. This district was protected by a hill from the direct radiation and blast effects, but did receive fallout described as "black rain" by Sztanyik. Any extra dose received by these early entrants cannot be quantified since no measurements could be made; yet, it may represent another instance where a "hidden dose" contributed to effects or complicated reconstruction of dosimetry from the instantaneous gamma and neutron fluxes.

Much of the evidence for a "hidden dose" is circumstantial. Yet, the efforts now under way to reconstruct the events of the years of atmospheric testing, particularly at NTS, will perforce have to take such factors into account. The effect may be small in many cases, but it cannot be dismissed.

C. Infant Mortality and Other Correlations

1. The Proposition

Professor Ernest Sternglass, a radiological physicist in the Department of Radiology at the University of Pittsburgh, entered the fallout arena indirectly in 1963, directly in 1968. At the 1963 Congressional hearings on fallout (pp. 410-417), Sternglass discussed the problems of the dose-response curve for low levels of ionizing radiation. He presented an analysis of data from the literature by MacMahon, the Harvard epidemiologist, and Alice Stewart and colleagues from the United Kingdom relating the number of intrauterine x rays taken during prenatal development to the incidence of leukemia in the children so irradiated. He concluded that effects appeared at doses of a few tens of millirad. As a spokesman for the Pittsburgh Chapter of the Federation of American Scientists, Sternglass pointed to the known greater sensitivity of the human embryo compared to the adult as a cause for concern about the doses from fallout radiation, including radionuclides taken internally (U.S. Congress 1963, p. 410).

(a) A generally long persistence of chromosome aberrations in the exposed Japanese had been established.

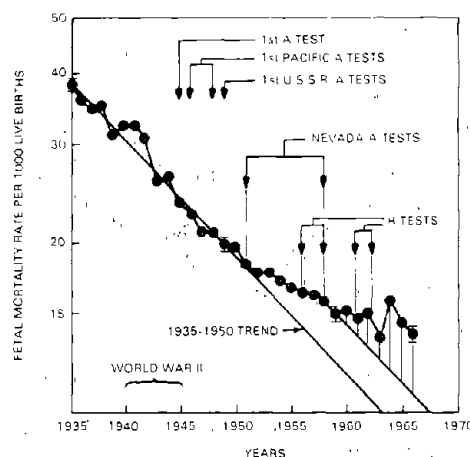
There was also a paper on the x-ray story in *Science* (Sternglass 1963) that reviewed the retrospective epidemiology studies of Stewart and of MacMahon.

There was nothing new about this qualitatively. The high sensitivity of the developing embryo and the production of gross physical or mental defects in both the irradiated individual and in future generations had been much studied by radiobiologists using animal data and was understood by clinicians. The probable doses for such effects were moderately well known, or so it was thought. It was the extremely low level of dose-effectiveness Sternglass proposed that was different. This conclusion was analyzed by many investigators, including those whose data Sternglass had used. The evidence for effects at such very low levels of x-irradiation was considered insufficient. The criticisms were sharp and perhaps made Sternglass wary of the traditional routes for scientific publication, for he turned away from them for much of his future work.

In the next years, Sternglass evidently spent much time with the help of graduate students and associates analyzing epidemiologic data of all kinds. In 1968, he entered the fallout controversy "in spades" with a series of presentations at scientific meetings, discussions, and presentations to the media and papers in periodicals such as the *Bulletin of the Atomic Scientists*, and the *Medical Tribune*. He essentially abandoned his work in radiological physics and began a crusade that varied in detail but continues to this day with the same basic tenets. This was temporal correlation of the two variables, infant mortality or leukemia incidence and low-level radiation. It began with fallout from weapons tests:

Infant mortality in the United States and much of the western world had been falling steadily since at least 1935. However, beginning at about the time of the first weapons tests, the rate of decline in infant mortality became less marked in nonwhite U.S. citizens. The same effect was seen a few years later in the total U.S. population and still later in the population of Sweden. The decline appeared to resume its old trend soon after the test ban of 1962. The typical picture as drawn by Sternglass is shown in figure 12.27. The change in slope of the mortality line was termed "excess mortality" by Sternglass and attributed by him without any question to the tests.

FIGURE 12.27. Fetal death rate for Missouri showing the "excess" over the expected rate based on the 1935-1950 regression line. Data from U.S. Vital Statistics. (Redrawn from Tomkins and Brown 1969, Sternglass's presentations.)



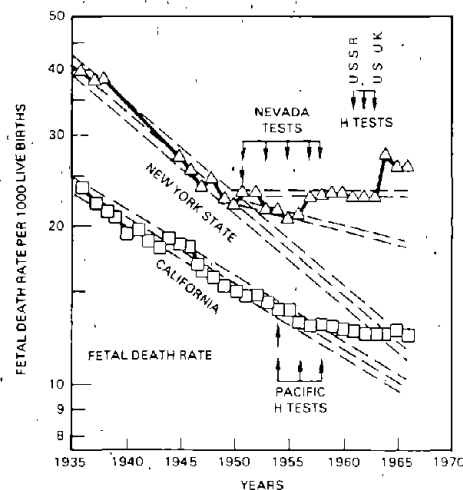
At the 1968 meeting of the Health Physics Society held in Denver, Sternglass presented specifics relating the fallout incident in Troy-Schenectady, New York to increased infant mortality. At the Hanford biology symposium in 1969, he showed data for excess numbers of cases of leukemia and of infant mortality on

a state-by-state basis, e.g., California, Missouri, and New York and later by cities, e.g., St. Louis, other cities to the east of the Trinity Site, etc.

At the 1969 meeting of the Health Physics Society held in Pittsburgh, Sternglass proposed correlations between levels of ^{90}Sr in milk and excess infant mortality. He proposed also that the ^{90}Sr was depositing in gonads and was responsible for genetic changes that could greatly reduce the numbers of children born in subsequent generations and increase the numbers of genetic defects.

The correlations always worked out in favor of the projected participation of fallout at the most logical time. For example, as detailed in figure 12.28, the change in fetal death rate was shown as beginning in New York State in tune with the Nevada tests, but did not appear in California until the large Pacific Proving Ground tests had generated fallout that could reach California in requisite quantity.

FIGURE 12.28. Fetal death rate reported per 1,000 live births versus time for New York State and California, before and after the onset of nuclear weapons tests in 1951. Symbols indicate the standard deviation due to statistical fluctuations alone. (Redrawn from Tomkins and Brown 1969 from presentations of Sternglass.)



As indicated, the early phases of Sternglass's crusade were largely through presentations at national scientific meetings. These were published as abstracts, but not as complete papers in the refereed journals. There were two papers in the *Bulletin of the Atomic Scientists* (Sternglass 1969c,d), two in the *Medical Tribune* (Sternglass 1969a,b), and an impassioned plea against the antiballistic missile (ABM) program that appeared in *Esquire* magazine (Sternglass 1969e).^(a)

The PHS in a sense assumed the burden of publication for Sternglass by presenting many of his original figures and arguments in an evaluation prepared by Tomkins and Brown (1969). The evaluation was done in response to the understandably intense reaction that the views propounded had in the biomedical community.

2. Critiques

Like all correlations based upon temporal associations, the scientific community wished to check out cause and effect as well as the facts themselves.

(a) The nature of the subjects addressed can be appreciated from the titles of these presentations and publications (see references). They included the prediction that no children would be born on this earth ever again if the ABM system were put in place and used. This was based upon the fact that the ABM was to be detonated at high altitude and the radionuclides would receive worldwide distribution from the stratosphere.

Note that nearly all of the elements of the crusade were mounted in 1968-1969, a very busy period for Dr. Sternglass and for all of the biomedical community, which had relaxed somewhat regarding fallout problems. Every aspect required checking out.

First, we should note that the doses involved were never quantitated except for the early work with x rays. It was Sternglass's view that the effects were due to doses far too low to be measured reliably. The thousandfold or more greater sensitivity of humans to low-level radiation that was Sternglass's primary thesis was not based on dosimetry but on the correlations between events. Radiobiologists are accustomed to relating effects to doses.

The chief areas brought into question can be put in three categories: (1) the source terms, (2) the epidemiology, and (3) the correlative basic radiobiology.

a. Questions Regarding the Source Terms

It was contended that the fallout frequently did not go where Dr. Sternglass said it did. This question was addressed in depth by John Harley of HASL in New York, the organization that had very intimate contact with the fallout measurements as we have seen in previous sections. We will begin with Harley's summary (Harley 1969) of the points he was addressing:

There are three ways in which Dr. Sternglass has used strontium-90 fallout for his correlations.

1. He stated that the fallout from the Trinity Test at Alamogordo in 1945 went from west to east across Texas, Arkansas, Louisiana, Mississippi, Alabama, Georgia and the Carolinas. He stated that there was no immediate effect but that an excess in infant mortality of up to one child per hundred live births occurred five years later.

2. He stated that excess infant mortality began to appear in 1950-1951 in the wet metropolitan states of Massachusetts, Pennsylvania, Illinois, and New York, and the wet rural states of Georgia, Mississippi, Missouri and Louisiana following nuclear tests in Nevada. On the other hand, the dry rural states of Wyoming, New Mexico, Idaho and Colorado did not show excess infant mortality until after the thermonuclear tests of 1954 and 1958. In both cases, he claimed that the "excess infant mortality" began as soon as fallout occurred.

3. He correlated his "excess infant mortality" for six states where strontium-90 in milk was measured by the Public Health Service from 1957 on. He also correlated the nation-wide "excess infant mortality" with the total amount of strontium-90 produced in weapons tests, with the average strontium-90 in U.S. milk and with the amount of strontium-90 deposited in the northern hemisphere.

(Harley 1969, p. I-3)

With regard to the use of fallout data for Trinity, Harley points out that:

The trajectory of the 1945 Alamogordo Test has been plotted for winds at the 10,000, 20,000 and 30,000 ft. levels. These would indicate that the majority of the fallout would have been deposited in New Mexico and that the cloud would have crossed the state towards the northeast, going into Kansas and Nebraska. The portion of the cloud at 30,000 ft. did start toward the southeast but turned back into Texas without crossing the Mississippi.

(Harley 1969, p. I-4)

Harley further cites the data from soil samples and the fact that they show no anomalies. Thus, in his opinion, there is no reason to suspect that the fallout pattern predicted by the trajectory is in error, and it is quite different from that stated by Sternglass.

Regarding the second use of fallout data, Harley points out that the distinction between "wet" and "dry" states was developed by the FRC (see section VII) to apply to stratospheric fallout. The pattern from the early Nevada tests was quite different. The general trajectory was from tropospheric winds (see sections V and VI). Some of the "dry" states in the FRC nomenclature received much more fallout from NTS than states designated as "wet." The ^{90}Sr deposition in the United States before 1954 as determined by HASL is shown in figure 12.29 (Harley 1969).

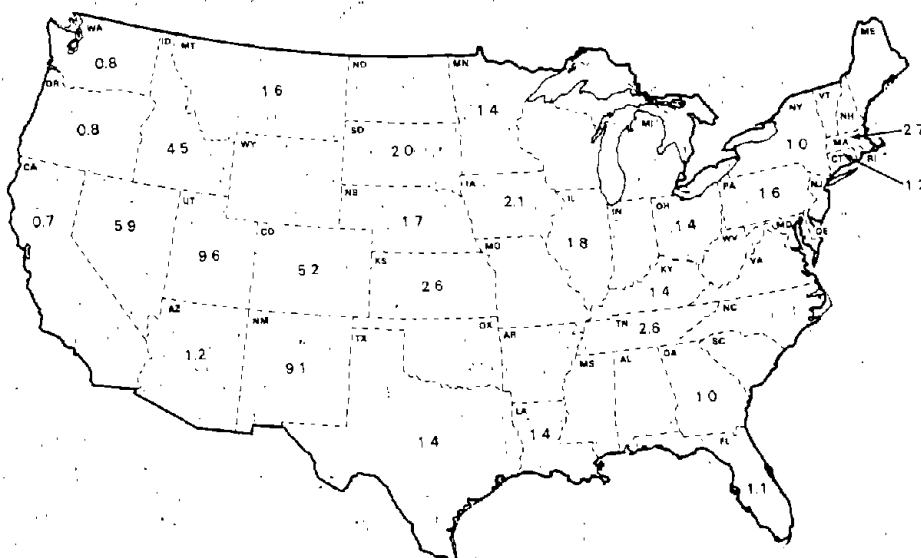


FIGURE 12.29. Strontium-90 deposition before 1954, based on gummed film measurements (mCi/m^2). (Redrawn from Harley 1969.)

Thus, there seem to be some curious inconsistencies in the data with regard to where the fallout went. Sternglass responded that he used information from the U.S. Weather Bureau and considered it equally reliable to that quoted by Harley. There is more of the same in other criticisms and rebuttals regarding the source term.

b. Epidemiologic Questions

Considering the data on milk, Harley was puzzled by the fact that the peak mortality rates Sternglass used lagged the peak concentrations in milk by five years, while "they supposedly follow ^{90}Sr deposition levels immediately in other graphs prepared by Dr. Sternglass" (Harley 1969, p. 1-7). As we will see below, the reported times of onset of the "excess mortality" were so variable that a logical epidemiologic study was very difficult.

Furthermore, in the report already cited, Harley comments that it is difficult to see how a test explosion the size of the Trinity shot could give rise to excess infant mortality at the level of one per hundred without the later test yields that

were a factor of 10^4 higher producing almost 100% mortality. There was also the fact that the mortality effect proposed by Sternglass occurred in 1950, five years after the Trinity shot. Since the heaviest period of fallout in the Northern Hemisphere occurred in 1962–1963, there should have been, for consistency, very high infant death rates in 1967–1968. In fact, the mortality rate was lower than that expected from the immediately preceding years. There were some particularly knotty problems regarding the data for New York State, especially the Albany-Troy area, which Sternglass had singled out as a clear example. Dr. Peter Greenwald, Director of the Bureau of Cancer Control of the New York State Department of Health, was asked to comment on the Albany-Troy data in connection with plans for a symposium of pediatricians. He stated in a letter (Greenwald 1969)^(a) that one of the key sources of data on the leukemia incidence in children, prepared by the New York State Health Department (Lade 1964), was in error. The questions raised are quoted below.

I would like to draw your attention to Table I^(b) of the *Science* article labeled "Cases of Leukemia in Children Under 15 Years of Age Reported in Albany, Rensselaer and Schenectady Counties, New York." While it is unfortunate that this Health Department may have erred in not clearly describing the possible inaccuracies in this table, it is clear that they should now be pointed out. The problems with these data and thus with the Sternglass paper are as follows:

1. The cases are listed by year of report. The year of report may well be different than the year of diagnosis, although I would judge by looking through a few case report cards in 1955 that the variation is not more than 1 or 2 years. There were two factors that could have influenced the quality of reporting in the early and mid-1950's. First, Dr. Kenneth Olson of the Albany Medical School began a registry for his hospital in 1952. Second, cancer case reports were not tabulated by the New York State Health Department in either 1954 or 1956. These are the only two years since 1940 that cases were not tabulated during the year of report. The reports for these two years were tabulated in retrospect in the early 1960's. The two above factors might influence year of report. They would probably not influence the total number of cases, since all persons who do not move after time of report should be identified through death certificates.

2. The place of residence refers to the residence of the child at the time the leukemia was reported. This may vary considerably from the place of residence of the mother at the time of the child's birth.

3. The year of birth for this table was derived by subtracting the reported age of the child with leukemia from the year in which the case was reported. This means that the year of birth could easily be off by one or more years.

4. In order to assess the extent of items 2 and 3 above, this Bureau examined the case reports, death certificates and birth certificates, when available, of the eight cases listed in table 1 as having been born in 1953. Two additional cases were identified who were born in the tri-county area in 1953 and who were reported to have leukemia after the time of the *Science* publication. The results of the review are shown in table A (enclosed). You will note that for only three of the eight cases did the mother reside in the tri-county area at the time of birth, and was the child truly born in 1953. Three of the remaining 5 persons were born in a different year—either 1952 or 1954; one was born in New Mexico; and one was born in a different county in New York State.

(a) There was also a full report by Greenwald and Kirsch entitled "Is There Evidence for an Association of Radioactive Fallout to Leukemia and Fetal Mortality in New York State?" but this author has only an undated manuscript copy of this.

(b) The tables referred to are shown as note 6 at the end of this chapter.

5. You will also note from table 1 that many of the cases have a lymphocytic histologic type, according to the case report card or the death certificate. It is my understanding that lymphocytic type leukemia has not definitely been associated with radiation exposure.

6. Case #2 (JP) was born by Caesarian section, raising the possibility of prenatal diagnostic X-ray exposure to this child. According to the birth certificate, case #2 was born after 37 weeks gestation and weighed 8 pounds. (Greenwald 1969)

Obviously, Sternglass could hardly be faulted for the fact that some of the mortality statistics he used were faulty. However, it appears that he was fully informed of the problems, yet never modified his position.

One of the more extensive analyses of the epidemiology was the one already cited sponsored by the PHS (Tomkins and Brown 1969). The report is too detailed for full description here, especially since there is no summary or conclusions. The last paragraph of the discussion section gives the flavor of the report:

The rate of decline of infant mortality in the United States did change around 1950. This lowering of the rate of decline has been a concern of many people working in the public health field. Many careful studies have been made, and no single factor nor group of factors have been identified which explain this change. While the hypothesis that this change is a result of ^{90}Sr deposition from fallout is an interesting one, the data presented do not appear to indicate any relationship between the change in rate of decline of infant mortality and the deposition of fallout in the United States.

Investigators in the United Kingdom entered the fray also. Lindop and Rotblat (1969) from the medical college of St. Bartholomew's Hospital in London examined each facet of the papers presented by Sternglass at the Hanford biology symposium and at the 1969 meeting of the Health Physics Society. They were puzzled among other things by the fact that, if it takes four years for the effect to manifest itself, why should it begin to decrease as soon as the ^{90}Sr began to decrease? A genetic effect would be expected to continue for a long time after cessation of the tests. They had problems with the statistics also.

Investigators in Canada were puzzled by the fact that although their ^{90}Sr levels were somewhat higher than in the United States, they did not seem to have any effect on infant mortality (Shaw and Smith 1970).

Other questions that were raised concerned the possible influence of other environmental factors, for example the presence of rubella and polio epidemics in 1953 and of measles and mumps epidemics in 1954 in Albany County, New York. These same types of problems were raised for other cities and states. They all come down to the problem of selection of a single factor from a galaxy of possible factors, one of the prime problems with retrospective epidemiology. Nevertheless, all that could be done was to point to the *possibility* that these other factors might play a role. There could be no solid proof for any single causative agent.

One of the more balanced reviews of the entire situation and the possible role of several environmental factors is contained in a critique by Arthur Tamplin and colleagues, then at the LLL. The abstract of this report is reproduced in its entirety below.

This report examines the data and conclusion of the Sternglass article in the May issue of the *Bulletin of Atomic Scientists*. In that article Sternglass purports to show that fallout radiation has increased infant and fetal mortality by 60 or more percent.

In this report, we undertake a critical review of that article and show that the data do not support his conclusions. This report demonstrates that the *major* factors influencing infant and fetal mortality over the past 50 years have been improving social-economic conditions and the introduction of antibiotics.

The available data on infant and fetal mortality and the supporting collateral data demonstrate that the worldwide differences in these mortality rates are a result of differing social-economic conditions. They indicate that the major factor that could improve the mortality rates in the United States is improvement of the social-economic conditions of the poor. They show that middle-class Americans enjoy the lowest mortality rates in the world and indicate that increased medical care would probably have little effect on the mortality rates of the poor; that an economic transfusion is needed, and that even then it would require at least a generation to bring the rates to parity.

At the same time, the existing experimental data indicate that fallout radiation probably did contribute to infant and fetal mortality by way of lethal mutations but nowhere near the effect suggested by Sternglass. The effect is most likely at least a factor of 100 smaller than he proposes. Moreover, in terms of non-lethal but deleterious mutations, the data suggest that it is now too early to look for the effect. This latter effect would be expected in 1980-1985 when the children born during the 1960-1965 era reach child-bearing age. It is impossible to estimate this aspect of the problem. Even then it might prove impossible to determine the effect from the death rate data because, in the 1980-1985 period, we may be observing the full brunt of the effect of the wide variety of environmental pollutants that have plagued this group of new parents from conception to child-bearing age. It may be that fallout radiation will represent only the top of the iceberg. (Tamplin, Ricker, and Longmate 1969)

c. Correlative Radiobiological Questions

Let us turn briefly to some nonepidemiologic considerations.

1. The genetic dose to man from ^{90}Sr is quite small compared to the dose to bone and bone marrow. Swedish work (Lüning et al. 1963a,b) did indeed implicate ^{90}Sr as a cause of fetal death in mice. However, Brues pointed out that this was due most probably to irradiation of the gonads by beta particles from the skeleton near the gonads, not from deposits of ^{90}Sr in the germ cells of the gonads. In man, the gonads are beyond the range of the beta rays produced from ^{90}Sr in bone. An alternative, direct genetic effect on the germ cells cannot be conclusively eliminated, except to say that no such effects have been seen in animal experiments at much higher doses.
2. Good experimental data with an important implication to the possible role of fallout and ^{90}Sr come from the large experiment with pigs at Hanford (see chapters 8 and 13), which were fed large doses of ^{90}Sr daily for years. Neither the parents nor their offspring exhibited effects on reproductive capacity, even at levels high enough to produce bone cancer, lymphoid disorders, etc. In fact, there were no malformations or stillbirths in the experiment. Dr. Sternglass takes the view that animal data are not pertinent, that only man shows the exquisite sensitivity to low-level radiation called for by his hypotheses.

3. Comment

Despite the volume and stridency of the critiques, Sternglass remained undaunted. He prepared rebuttals for many of the points, which can be reviewed in his book issued in 1972 (Sternglass 1972a). If things seemed to be going badly for one set of data, he would frequently appear with analyses applied to new

situations, but using the same basic techniques and arguments. Thus, as the fallout issues receded, he applied the same general approach to emissions from nuclear power plants and cited excess infant mortality around operating nuclear reactors as well as many other facilities involving radiation or radioactive materials.

He became interested in the cell membrane and proposed effects of very low-level radiation doses on it in a paper at the fourteenth Hanford biology symposium (Sternglass 1976). It is getting us too far from radionuclides and fallout to go further here, except to remark that some implications of the membrane effects were discussed by Stannard in the same volume (Stannard 1976).

The Sternglass crusade was extended to questioning the adequacy of the AEC's limits for exposure of the public to effluents from nuclear facilities, an area where Dr. Sternglass had much more company than he did for his fallout proposals. The data used concerned infant mortality around the Dresden I reactor in Illinois, the Big Rock Point facility in Michigan, the Humboldt Bay installation in California, the Indian Point plant and BNL in New York, and others. Most of these were presented at hearings or other legislative investigations and at a meeting of the Association of Physicists in Medicine (Sternglass 1972b). The references for the hearings presentation can be seen in two BNL reports (Hull and Shore 1971 and 1972), which include the usual critiques of the way the data were gathered and handled.

What conclusions can be drawn from all this? It must be obvious that there were and are many problems with the way the data were analyzed in attempts to support the hypotheses as well as with the data themselves. Yet, it is also obvious that Sternglass stimulated a comprehensive examination of infant and child mortality in the United States. Indeed, many of the problems with the data might never have been discovered except for the stimulus of his crusade.^(a) No one can prove conclusively that he is wrong, only that much more information would be needed to prove that he is right. An expression of this can be seen in the concluding paragraph of an editorial on Sternglass's work published in the McGraw Hill periodical *Scientific Research* (H.L.D. 1969).

The upshot of all this is that apparently no one has done a large-scale animal experiment with ingested Sr^{90} at the fallout dose levels the results of which could then be used to directly prove or disprove Sternglass's hypothesis. Until someone does we can not be completely certain that some unthought-of low-level effect does not exist. As Dyson expressed it, "The essential point is that we do not have a firm upper limit to the infant mortality caused by fallout. Although Sternglass's argument may be 'sloppy' we have no proof that his conclusion is wrong."

This was in 1969. Has work over the intervening years provided conclusive answers? In a sense it has to the degree that the exquisite sensitivity proposed by Sternglass has not yet appeared in experimental work. Yet, all experiments are at higher doses, and an inhibiting effect of these higher doses cannot be

(a) These statements should not be interpreted as indicating that the whole episode was a net gain. The value of the research interrupted or never done in other areas while investigators dropped everything to respond to Sternglass's allegations can never be ascertained. In this author's opinion, it would be considerable. Nevertheless, we cannot gainsay attempts to salvage something of value to science from the enormous volume of attacks and counterattacks involved.

conclusively denied. It would take an experiment with millions of animals to do what is required in the editorial just quoted.

Let us conclude by quoting from an extensive comment by Boffey in the "News and Comment" section of *Science* (Boffey 1969).

The Sternglass case has raised the perplexing question of whether it is "good" or "bad" to have a scientist yelling "fire" when there may not be any fire at all. On the negative side, some critics contend that Sternglass, by alarming the public without reason, has made it more difficult to reach rational decisions on such important issues as the ABM and nuclear power. Others contend that, if Sternglass is ultimately shown to be a fool, the public's confidence in the scientific method will be diminished. And if Sternglass has actually made selective use of the data to support a preconceived theory—as some critics allege—that, of course, cannot be defended.

On balance, however, the country probably has more to gain than lose by letting Sternglass have his day in court. If Sternglass is right, he has performed an incalculable public service. But even if he is wrong—and the weight of informed opinion seems to think he is—he has nevertheless served a useful function by forcing others to look into the question.

We have already commented earlier and will again in chapter 21 on the surprising lack of experimental work on the genetic effects of deposited radionuclides. Only recently has serious work in reasonable volume been brought to bear in this area.

D. Progress

It is easy to cite in extenso the problems and dilemmas brought upon us by the testing of nuclear weapons, especially if one is writing from the standpoint of the biomedical community. It is more difficult to cite scientific and technical progress that was made as a result of the enterprise. Most of the progress is in the realm of basic research and has been described in earlier chapters or will be in chapters 13, 15, 21, and elsewhere. For the moment, let us list a few areas of pertinence.

1. Weapons Design and Efficiency

This area should be the one where the testing enterprise produced the greatest technical progress. It is, of course, one we cannot discuss.

2. Movement of Radioisotopes in the Biosphere and Geosphere

While much information was gathered in connection with effluents from nuclear installations, there can be no doubt that the worldwide distribution of fallout radionuclides enabled the collection of information on ocean currents, the behavior of radionuclides in the sea, patterns of air distribution, the exchange phenomena between troposphere and stratosphere, latitude effects, etc., that would never have been obtained otherwise.

3. The Behavior of Radioisotopes in the Food Chain

Again, some information could have been gathered from deliberate experimental contaminations. Some was obtained in work around nuclear energy installations. But the decisive role of food-chain transfer processes came to light from the fallout investigations.

4. Behavior of Radionuclides in Animals and Plants and in Humans

Much of this work has been described in earlier chapters, or will be in chapter 13. Much was done without the stimulus of fallout. Yet, the large increases in resources and manpower thrown into the field made a significant difference in both the rate of accrual and extent of our knowledge. Some of the most interesting work involving discrimination factors, the movement of pairs of isotopes, the important role of chemical forms of both the radionuclide and the receptor might never have been done without the stimulus of the fallout problems.

5. Radioecology

Examination of the development of radioecology described in chapter 11 makes it clear that the field was considerably advanced by the work involving fallout, even though it had its beginnings in work around nuclear energy sites.

6. Biological Effects of Deposited Radionuclides

Much of our knowledge of the effects of deposited radionuclides was already accrued when the fallout problems came upon the scene. The major large experiments were already under way with some exceptions. Yet, there can be no doubt that all such work was better supported and stimulated more interest because of the problems of fallout from testing of nuclear weapons. In the next chapter, we will review briefly some of the biomedical research that can be characterized as arising out of the problems of fallout.

IX. Summary and Commentary

Of the three new dimensions designated in this book for overt discussion, this third one was perhaps the least anticipated or prepared for and had the widest consequences beyond the world of science. The possibility of phenomena we now designate as fallout was definitely considered before the first nuclear weapons test at Alamogordo, New Mexico. Teams were outfitted to try to follow the fission product cloud. Preparations were even made to evacuate one or more of the nearest towns if needed. This was found unnecessary, but the existence of fallout and of residual contamination was fully established by this very first shot.

Fallout played a minor role in the bombings of Japan, although it was not completely absent. The detonations were at sufficiently high altitude to avoid contact of the fireball with the earth's surface. Perhaps for this reason, the phenomena of fallout came as more of a surprise when the weapons testing program began than they would have otherwise.

Operation Crossroads, in July 1946, opened everyone's eyes to the potential for contamination from fallout. The underwater shot (Test Baker) rained tons of highly radioactive water on the test fleet and made the ships uninhabitable for appreciable periods. In the U.S. Navy, it generated the need for a laboratory to concentrate on such contamination phenomena. Thus, the NRDL was organized and launched.

When it became clear that the United States no longer had a monopoly on atomic energy and atomic weapons, the central Pacific area, instead of shutting down, became the "Pacific Proving Grounds," and a continental site, the

"Nevada Test Site," was developed for "smaller" devices to reduce the problems of transportation over many thousands of miles. Nearly 300,000 kt of energy equivalent were released in airborne tests beginning in 1945, and the problems of fallout inevitably followed.

As part of these activities, resurveys were conducted early of sites such as Bikini (Operation Crossroads) and Alamogordo (Trinity shot). Biologists from the University of Washington were especially active in the former; personnel from UCLA in the latter. They found that the Trinity fallout had gone considerably farther than the original measurements indicated. Even a year after the operation, contamination of the Bikini lagoon and its biota was far from negligible, and the concentrations in certain aquatic forms was found to be quite high.

In theory, it was thought that the fallout from the fission tests at NTS would remain largely onsite. This was, of course, found to be quite wrong. Not only were there the incidences of contamination of communities in Nevada and Utah and entry of fallout radionuclides into food chains, particularly milk, but the clouds occasionally traveled across the entire country and produced local rain-out or snow-out in the northeastern sections in line with prevailing weather patterns.

With the advent of the testing of thermonuclear weapons, the dimensions of the fallout problem were widened enormously. These devices had enough energy to inject radioactive products into the stratosphere, where they were retained for appreciable periods and gradually distributed latitudinally as well as longitudinally. Thus began the problems of worldwide fallout from nuclear weapons tests, with movement in the upper atmosphere and gradual exchange between stratosphere and troposphere, all added to the tropospheric movement known earlier. The biomedical significance of ^{89}Sr and ^{90}Sr and of iodine in air and in food and water and other radionuclides in the environment required enormous efforts at collection and analysis (this chapter) and experimental studies of effects (chapter 13). Indeed, the biomedical community found itself in the midst of a first-class crisis, where knowledge fell far short of needs.

The importance of fallout was especially underscored by the notorious Shot Bravo in the Castle series in the Pacific. This was the thermonuclear shot that contaminated the Marshall Islands and many of the inhabitants, as well as U.S. servicemen, the Japanese fishing boat *Lucky Dragon*, and produced an uproar in Japan regarding potential contamination of their seafood sources.

From this point on, scientific problems of fallout, both its behavior and effects, had to be explored side-by-side with growing political, even moral, issues. Many of these led eventually to litigation both in the continental United States and in the Pacific and enormously expensive efforts concerning the repatriation of the Marshallese and the care of those who had been exposed. These events are described in moderate detail, including all but the most recent decisions and actions.

Despite the strident nonscientific problems, including debates on whether or not testing should ever have been engaged in at all, much new scientific knowledge was gained as a result of all of these efforts. In chapter 13, we will review much of the *de novo* research stimulated by the problems of fallout. Yet, much was also learned in the field work described herein. The kinetics of movement of radionuclides in local, regional, and worldwide environments were studied with an intensity undreamed of before. This included atmospheric transport phenomena, aquatic transport, and the more obvious terrestrial systems. Unlike the experiments involving the acute effects of external radiation from the shots,

the potential for effects from radionuclides came in for much longer-term study. In fact, it is the potential of these early exposures for producing cancer decades later that now sustains attention on the problems of fallout, even though the amounts now remaining are very small.

The chapter digresses slightly from the central theme with a discussion of the standards developed for exposure to fallout, including whether or not the common practice of assuming that protection against the external radiation dose really sufficed to protect against the effects of long-term exposure via deposited radionuclides. Also, the allegations of E. Sternglass, which began around a proposed correlation between infant mortality in various sections of the United States and exposure to fallout radionuclides, are reviewed in some depth.

The chapter concludes with a listing of some of the positive correlates of this enormous endeavor. Naturally, what we learned concerning one of the primary reasons for the tests, i.e., weapons design and efficiency, cannot be discussed or evaluated since the information remains unavailable to the public, including the biomedical community.

Note 1

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Note 6

Tables excerpted and modified slightly from letter by Peter Greenwald (1969)
 [see text, section VIII C]

Table A. Eight Persons Who Developed Leukemia Who are Listed by Sternglass as Being Born in 1953 and Residing in Albany, Schenectady or Rensselaer Counties and Two Later Cases

Initials	Date of Birth	Residence of Mother at Time of Birth (County or State)	Year of Leukemia Report	Histologic Type from Death Certificate or Case Report Card	Father's Occupation from Birth Certificate	Remarks
A. Cases truly born in 1953 with mother residing in tri-county area.						
1. WR	3/27/53	Rensselaer	1954	Lympho-blastic	Machine Operator, Watervliet Arsenal	
2. JP	6/8/53	Albany	1960	Acute Leukemia	Mechanic-Chemical	Caesarean Birth
3. EW	8/25/53	Albany	1956	Leukemia	Tool Grinder, Watervliet Arsenal	
B. Cases truly born in a year other than 1953, or mother residing outside tri-county area.						
4. MG	5/23/52	Schenectady	1962	Acute Lymphocytic	Accumulator, General Electric	
5. DA	5/25/52	Albany	1956	Acute Lymphatic	Painter-Mechanic, NY Central RR	
6. DC	3/12/54	Albany	1957	Acute Lymphocytic	Foreman, Coleman Heal & Wedge Co.	
7. CP	5/31/53	New Mexico(a)	1957	Acute Lymphatic	Unknown	

TABLE A. Continued

Initials	Date of Birth	Residence of Mother at Time of Birth (County or State)	Year of Leukemia Report	Histologic Type from Death Cert. or Case Report Card	Father's Occupation from Birth Certificate	Remarks
8. DS	8/9/53	Montgomery Co., NY	1961	Lympho-blastic	Machinist, General Electric	
C. Cases truly born in 1953 with mother residing in tri-county area and not reported by Dr. Sternglass.						
9. HW	9/27/53	Schenectady(b)	1964	Acute Granulocytic	Unknown	Adopted Child
10. RG	11/6/53	Albany	1965	Granulocytic	Printer, Williams Press	

(a) Place of birth of child; mother's residence at time of birth unknown.

(b) Place of birth of child; mother's residence at time of birth unknown because of adoption.

Table B. Number of Cases of Selected Infectious Diseases Reported to the Albany County Health Department, 1951-1955

Disease	1951	1952	1953	1954	1955
Rubella	29	104	994	108	21
Measles	2459	437	100	1268	1529
Chicken Pox	487	486	614	634	596
Mumps	277	108	208	500	51
Hepatitis	14	3	212	390	73
Polio	23	8	46	25	24

References

- AEC. See Atomic Energy Commission.
- Alexander, L. T., E. P. Hardy, Jr., and H. L. Hollister. 1960. Radioisotopes in soil: particularly with reference to strontium. In *Radioisotopes in the biosphere*, eds. R. S. Caldecott and L. A. Snyder, pp. 3-22. Proceedings of a symposium held in Minneapolis, October 19-23, 1959, Minneapolis: Univ. of Minn., Center for Continuation Study.
- Allred, D. M. and D. E. Beck. 1963. Comparative ecological studies of animals at the Nevada Test Site. In *Proceedings of the 1st national symposium on radioecology*, eds. V. Schultz and A. W. Klement, Jr., pp. 327-31. Held at Colo. State Univ., September 1961. New York: Reinhold Publishing Co.; Washington, D.C.: American Institute of Biological Sciences.
- Anderson, E. C., R. L. Schuch, W. R. Fisher, and W. Langham. 1957. Radioactivity of people and foods. *Science* 125:1273-78.
- Andrews, H. L. 1955. Radioactive fallout from bomb clouds. *Science* 122:453-56.
- Andrews, H. L. 1980. Taped interview at Jamestown, R. I., September 27, 1980.
- Andrews, H. L. 1985. Letters to J. N. Stannard dated January 16 and March 5, 1985.

- Anspaugh, L. R. 1979. Letter to Tommy McCraw, U.S. Department of Energy, commenting on an early draft of Shleien's paper. [From DOE files, Washington, D.C.]
- Atomic Energy Commission. 1954. News release, March 11, 1954, 2:00 p.m., Washington, D.C.
- Atomic Energy Commission. 1955. *The effects of high-yield nuclear explosions*. Statement by L. L. Strauss, chairman, and a report of the U.S. Atomic Energy Commission. Washington, D.C., February 1955.
- Atomic Energy Commission. 1956. *Some effects of ionizing radiation on human beings. A report of the Marshallese and Americans accidentally exposed to radiation from fall-out and a discussion of radiation injury in the human being*, eds. E. V. Cronkite, V. P. Bond, and C. L. Dunham. July 1956.
- Atomic Energy Commission. 1974. *Recommendations of AEC Task Group on Recommendations for Cleanup and Rehabilitation of Eniwetok Atoll*, April 19, 1974.
- Bair, W. J., J. W. Healy, and B. W. Wachholz. 1979. *Ailin in Enewetak Rainin: The Enewetak Atoll today*. Washington, D.C.: U.S. Department of Energy.
- Bair, W. J., J. W. Healy, and B. W. Wachholz. 1980. *Melelen radiation ilo ailiñ in Bikini: The meaning of radiation at Bikini Atoll*. DOE/TIC-11222. Washington, D.C.: U.S. Department of Energy.
- Bair, W. J., J. W. Healy, and B. W. Wachholz. 1982. *Melelen radiation ilo ailiñ ko ituiñ ilo Majöl, kó rar etali ilo 1978: The meaning of radiation for those atolls in the northern part of the Marshall Islands that were surveyed in 1978*. DOE/NBM-1052. Washington, D.C.: U.S. Department of Energy.
- Bair, W. J., R. O. McClellan, R. C. Thompson, W. E. Ogle, V. E. Noshkin, J. H. Harley, C. W. Francis, W. L. Templeton, J. E. Trimble, and J. W. Healy. 1977. Letter to James L. Liverman, Assistant Administrator for Environment and Safety, U.S. ERDA, on possible cleanup of Eniwetok Atoll, dated August 17, 1977.
- BARC. See Bikini Atoll Rehabilitation Committee.
- Barmash, L., J. W. Neel, W. K. Vance, III, H. M. Moore, and K. H. Larson. 1958. *Distribution and characterizations of fall-out in airborne activity from 10 to 160 miles from ground zero*. Operation Teapot report. WT1178, dated September 1958, declassified May 22, 1959.
- Bastian, R. K. and W. B. Jackson. 1975. ^{137}Cs and ^{60}Co in a terrestrial community at Enewetak Atoll. In *Radioecology and energy resources*, ed. C. E. Cushing, Jr., Ecological Society of America special publ. no. 1, pp. 314-20. Proceedings of the 4th national symposium on radioecology held at Oreg. State Univ., May 12-14, 1975. Stroudsburg, Pa.: Dowden, Hutchinson, and Ross, Inc.
- Beck, H. L. and P. W. Krey. 1983. Radiation exposures in Utah from Nevada nuclear tests. *Science* 200:18-24.
- Bellamy, A. W. et al. 1949. *The 1948 radiological and biological survey of areas affected by the first atomic bomb detonation*. AEC report UCLA-32, Washington, D.C.: U.S. Atomic Energy Commission.
- Beninson, D. 1974. Population doses resulting from radionuclides of worldwide distribution. In *Population dose evaluation and standards for man and his environment*, pp. 227-33. Proceedings of a symposium held at Portorož, Yugoslavia, May 20-24, 1974. Vienna: International Atomic Energy Agency.
- Bikini Atoll Rehabilitation Committee. 1984. *Resettlement of Bikini Atoll: Feasibility and estimated cost of meeting the federal radiation protection standards*. Report no. 1 submitted to U.S. Congress, November 15, 1984. Berkeley, Calif.
- Bikini Atoll Rehabilitation Committee. 1985. *Resettlement of Bikini Atoll: Feasibility and estimated cost of meeting the federal radiation protection standards*. Berkeley, Calif.
- Blatz, H. and L. R. Solon. 1953. *Estimation of lung dose from the radioactive cloud associated with a nuclear detonation*. AEC report NYO-4507. Official use only. Washington, D.C.: U.S. Atomic Energy Commission.
- Boffey, P. M. 1969. Ernest J. Sternglass: Controversial prophet of doom. *Science* 166:195-200.
- Bond, V. P. 1981a. The cancer risk attributable to radiation exposure: Some practical problems. *Health Phys.* 40:108-11.

- Bond, V. P. 1981b. *The radiation exposure compensation act of 1981*. Testimony before the U.S. Senate Committee on Labor and Human Resources, October 27, 1981.
- Bond, V. P. 1982. The radiation exposure compensation act of 1981. In *Newsletter of Health Physics Society*, vol. 10, no. 1, January 1982.
- Book, S. A. and M. Goldman. 1983. *Radioactive fallout: An overview of internal emitter research in the era of atmospheric nuclear weapons testing*. UCD 472-505. Springfield, Va.: National Technical Information Service.
- Booker, D. V. 1958. *Physical measurements of activity in samples from Windscale*. AERE HP/RE607. U.K.: Atomic Energy Research Establishment Report.
- Booth, A. H. and E. R. Samuels. 1969. Fall-out strontium-90 levels in Canada. In *Environmental contamination by radioactive materials*, pp. 393-402. Proceedings of a symposium held March 24-28, 1969. Vienna: International Atomic Energy Agency.
- Bost, W. E., H. E. Vorees, and N. K. Smelcer. 1961. *Radioactive fallout: A bibliography of the world's literature*. TID-3086. Washington, D.C.: U.S. Atomic Energy Commission, Division of Technical Information.
- Brauner, J. 1947. *Trinity survey program, August 1947—Mammal group*. U.S. Atomic Energy Commission classified report dated November 17, 1947, declassified February 29, 1972.
- Broseus, R. W. 1970. Cesium-137/strontium-90 ratios in milk and grass from Jamaica. Master's thesis, N.Y. Univ. [Cited by Eisenbud 1972, p. 382.]
- Bruce, R. S., B. O. Bartlett, and R. S. Russell. 1967. Time course of the transfer of strontium-90 through food chains to man. In Lenihan, Loutit, and Martin 1967, pp. 33-39.
- Bruce, R. S. and R. S. Russell. 1969. Agricultural aspects of acute and chronic contamination situations. In *Environmental contamination by radioactive materials*, pp. 79-89. Proceedings of a symposium held in Vienna, March 24-28, 1969. Vienna: International Atomic Energy Agency.
- Bustad, L. K., S. Marks, N. L. Dockum, D. R. Kalkwarf, and H. A. Kornberg. 1953. *A comparative study of Hanford and Utah range sheep*. HW-30119. Richland, Wash.: Hanford Atomic Products Operation.
- Caldwell, G. G., D. B. Kelley, and C. W. Heath, Jr. 1980. Leukemia among participants in military maneuvers at a nuclear bomb test: A preliminary report. *J. Am. Med. Assoc.* 244:1575-78.
- California Medical Association. 1983. Draft memorandum. Use of potassium iodide following a nuclear power plant accident. [Prepared for review by several advisory panels of the CMA, San Francisco, and dated November 29, 1983.]
- Carter, M. W. 1980. Off-site health and safety for nuclear weapons tests. In *Health physics: A backward glance*, eds. R. L. Kathren and P. L. Ziemer, pp. 197-215. New York-Oxford: Pergamon Press.
- Carter, M. W. and A. A. Moghissi. 1977. Three decades of nuclear testing. *Health Phys.* 33:55-71.
- Clark, H. M. 1954. The occurrence of an unusually high-level radioactive rainout in the area of Troy, N.Y. *Science* 119:619-22.
- Clusen, R. C. 1980. Letter from Assistant Secretary for Environment, U.S. Department of Energy, to J. J. Joseph, Undersecretary for the Interior, in regard to resettlement of the Bikini people on Eneu Island, dated May 1980.
- CMA. See California Medical Association.
- Code of Federal Regulations. 1972. Appendix B, table II to the Code of Federal Regulations, title 10, pt. 20, pp. 71-74a and b, as amended December 1972.
- Cohn, S. H. 1956. Persistence of radioactive contamination in animals of Marshall Islands two years after Operation Castle. In *The shorter-term biological hazards of a fall-out field*, eds. G. M. Dunning and J. A. Hilcken, pp. 211-18. Proceedings of a symposium held December 12-14, 1956. Washington, D.C.: Atomic Energy Commission.
- Cohn, S. H. 1982. Taped interview at Brookhaven National Laboratory, September 16, 1982.
- Cohn, S. H. 1983. Telephone conversation, November 14, 1983.

- Cohn, S. H., J. S. Robertson, and R. A. Conard. 1960. Radioisotopes and environmental circumstances: The internal radioactive contamination of a Pacific island community exposed to local fallout. In *Radioisotopes in the biosphere*, eds. R. S. Caldecott and L. A. Snyder, pp. 306-30. Proceedings of a symposium held in Minneapolis, October 19-23, 1959. Minneapolis: Univ. of Minn., Center for Continuation Study.
- Comar, C. L., B. F. Trum, U. S. G. Kuhn III, R. H. Wasserman, M. M. Nold, and J. C. Schooley. 1957. Thyroid radioactivity after nuclear weapons tests. *Science* 126:16-18.
- Commoner, B. 1958. The fallout problem. *Science* 127:1023-26.
- Conard, R. A. 1956. The effects of fall-out radiation on the skin. Presented at an AEC-DoD symposium, held December 12-14, 1956. In *The shorter-term hazards of a fall-out field*, eds. G. M. Dunning and J. A. Hilcken, pp. 135-42. Proceedings of a symposium held December 12-14, 1956. Washington, D.C.: Atomic Energy Commission.
- Conard, R. A. 1961. The biological hazard of a fall-out field. In *Radioactivity in man*, ed. G. Meneely. Springfield, Ill.: Charles Thomas.
- Conard, R. A. 1977. Survey of thyroid findings in Marshallese 22 years after exposure to radioactive fall-out. In *Radiation associated thyroid carcinomas*. New York: Grune and Stratton, Inc.
- Conard, R. A. et al. 1956. Medical survey of Marshallese two years after exposure to fallout radiation. BNL-412(T-80). Upton, N.Y.: Brookhaven National Laboratory.
- Conard, R. A. et al. 1957. March 1957, medical survey of Rongelap and Utirik people three years after exposure to radioactive fallout. BNL-501. Upton, N.Y.: Brookhaven National Laboratory.
- Conard, R. A. et al. 1958. Medical survey of Rongelap people, March 1958, four years after exposure to fallout. BNL-534(T-135). Upton, N.Y.: Brookhaven National Laboratory.
- Conard, R. A. et al. 1960. Medical survey of Rongelap people five and six years after exposure to fallout [with an addendum on vegetation]. BNL-609(T-179). Upton, N.Y.: Brookhaven National Laboratory.
- Conard, R. A. et al. 1962. Medical survey of Rongelap people seven years after exposure to fallout. BNL-727(T-260). Upton, N.Y.: Brookhaven National Laboratory.
- Conard, R. A. et al. 1963. Medical survey of Rongelap people eight years after exposure to fallout. BNL-780(T-296). Upton, N.Y.: Brookhaven National Laboratory.
- Conard, R. A. et al. 1963-1964. Medical survey of the people of Rongelap and Utirik Islands nine and ten years after exposure to fallout radiation (March 1963 and March 1964). BNL-908 (T-371). Upton, N.Y.: Brookhaven National Laboratory.
- Conard, R. A. et al. 1967 (1965-1966). Medical survey of the people of Rongelap and Utirik Islands eleven and twelve years after exposure to fallout radiation (March 1965 and March 1966). BNL-50029 (T-446). Upton, N.Y.: Brookhaven National Laboratory.
- Conard, R. A. et al. 1970 (1967-1969). Medical survey of the people of Rongelap and Utirik Island thirteen, fourteen, and fifteen years after exposure to fallout radiation (March 1967, March 1968, and March 1969). BNL-50220 (T-562) [summary document]. Upton, N.Y.: Brookhaven National Laboratory.
- Conard, R. A. et al. 1975. A twenty-year review of medical findings in a Marshallese population accidentally exposed to radioactive fallout. BNL-50424. Upton, N.Y.: Brookhaven National Laboratory.
- Conard, R. A. et al. 1980. Review of medical findings in a Marshallese population twenty-six years after accidental exposure to radioactive fallout. BNL-51261. Upton, N.Y.: Brookhaven National Laboratory.
- Conard, R. A., W. W. Sutow, B. P. Cokock, B. M. Dobyns, and D. E. Paglia. 1969. Thyroid nodules as a late effect of exposure to fallout. In *Radiation-induced cancer*, pp. 325-36. Proceedings of a symposium held at Athens, April 28-May 2, 1969. Vienna: International Atomic Energy Agency.
- Cronkite, E. P., V. P. Bond, R. A. Conard, N. R. Shulman, R. S. Farr, S. H. Cohn, C. L. Dunham, and L. E. Browning. 1955a. Response of human beings accidentally exposed to significant fall-out radiation. *J. Am. Med. Assoc.* 159:430-34.

- Cronkite, E. P. et al. 1955b. *Twelve month postexposure survey on Marshallese exposed to fallout radiation*. BNL-384 (T-71). Upton, N.Y.: Brookhaven National Laboratory.
- Dahl, A. H., R. Bostrum, R. C. Patzer, and J. C. Villforth. 1963. Patterns of I^{131} levels in pasteurized milk network. *Health Phys.* 9:1179-85.
- Daly, T. M. 1986. Crossroads at Bikini. In *Proceedings of the U.S. Naval Institute*, 112/71/1001:65-74.
- Deal, J. 1979, 1980. Taped personal interviews on March 16, 1979 and March 31, 1980.
- Dehos, R. and G. Kistner. 1980. Strontium-90 content in human bone of West German residents. *Health Phys.* 39:682-83.
- Denham, D. H. and D. A. Waite. 1982. Action guides and countermeasures. In *CRC handbook of environmental radiation*, ed. A. W. Klement, Jr., pp. 187-204. Boca-Raton, Fla.: CRC Press, Inc.
- Department of Health, Education, and Welfare. 1967. *Full-scale system for removal of radiostrontium from milk*. U.S. DHEW, Environmental Health Series, publication 999-RH-28, 99. Washington, D.C.: U.S. Public Health Service.
- DHEW. See Department of Health, Education, and Welfare.
- Dickson, D. 1983. Britain to study health effects of nuclear tests. *Science* 219:370-71.
- Dolphin, G. W. and W. G. Marley. 1969. Risk evaluation in relation to protection of the public in the event of accidents at nuclear installations. In *Environmental contamination by radioactive materials*, pp. 241-54. Proceedings of a symposium held at Vienna, March 24-28, 1969. Vienna: International Atomic Energy Agency.
- Dunn, D. B. and R. P. Levine. 1947. *Trinity survey program, August 1977, botany survey group*. Classified AEC report dated November 17, 1947, declassified February 29, 1972.
- Dunning, G. M. 1956. Two ways to estimate thyroid dose from radioiodine in fallout. *Nucléonics* 14(2):38-41.
- Dunning, G. M., ed. 1957a. Radioactive contamination of certain areas in the Pacific Ocean from nuclear tests. In *A summary of the data from the radiological surveys and medical examinations*. Washington, D.C.: U.S. Atomic Energy Commission, Superintendent of Documents, U.S. Government Printing Office.
- Dunning, G. M. 1957b. Radiological safety criteria during nuclear weapons testing at the Nevada Test Site. In *U.S. Congressional Hearings. Radioactive fallout and its effects on man*, vol. 2, pp. 248-60.
- Dunning, G. M. 1958. Radiation exposures from nuclear tests at the Nevada Test Site. *Health Phys.* 1:255-67.
- Dunning, G. M. 1959. *Report from division of biology and medicine*. TID-5551. Washington, D.C.: U.S. Atomic Energy Commission.
- Eisenbud, M. 1957. Global distribution of strontium-90 from nuclear detonations. *Scientific Monthly* 84:237-44.
- Eisenbud, M. 1973. *Environmental radioactivity*, 2d. ed. New York-London: Academic Press.
- Eisenbud, M. 1976. An environmentalist in the early days of atmospheric weapons testing. [Presented as part of a joint Health Physics Society-Radiation Research Society historical symposium, held in San Francisco, July 1976. Although never published, a tape was made and the author has used a transcript of the tape, as recorded by R. L. Kathren. Permission to refer to the speech and to use some of the photographs was granted by Dr. Eisenbud on August 16, 1979.]
- Eisenbud, M. 1979. Taped personal interview, July 9, 1979.
- Eisenbud, M. and J. H. Harley. 1953. Radioactive dust from nuclear detonations. *Science* 117:141-47.
- Eisenbud, M. and J. H. Harley. 1956. Radioactive fallout through September 1955. *Science* 124:251-55.
- Eisenbud, M. and M. E. Wrenn. 1963. Biological disposition of radioiodine: A review. *Health Phys.* 9: 1133-39.
- Eisenbud, M., Y. Mochizuki, A. S. Goldin, and G. R. Laurer. 1962. Iodine-131 dose from Soviet nuclear tests. *Science* 136:370-74.

- Ellis, W. S. 1986. Bikini: A way of life lost. *Nat. Geog. Mag.* 169:813-34.
- Enstrom, J. E. 1979. Fallout-radiation danger is a great cloud of doubt. *Los Angeles Times*, October 16, 1979.
- Enstrom, J. E. 1980. *The nonassociation of fallout radiation with childhood leukemia in Utah*. From the Baneberry Report 4, J. Carris, J. L. Lynn and M. Skolnick, Cold Spring Harbor Report (1980). [Cited by Bond 1981.]
- Environmental Protection Agency. 1976. *National interim primary drinking water regulations*. EPA-570/976-003. Washington, D.C.: U.S. Environmental Protection Agency, Office of Water Supply.
- EPA. See Environmental Protection Agency.
- FASEB. See Federation of American Societies for Experimental Biology.
- Federal Radiation Council. 1960. *Background material for the development of radiation protection standards*. FRC report no. 1, May 13, 1960. Washington, D.C.
- Federal Radiation Council. 1961. *Background material for the development of radiation protection standards*. FRC report no. 2, September 1961. Washington, D.C.
- Federal Radiation Council. 1962. *Health implications of fallout from nuclear weapons testing through 1961*. FRC report no. 3, May 1962. Washington, D.C.
- Federal Radiation Council. 1963. *Estimates and evaluation of fallout in the United States from nuclear weapons testing conducted through 1962*. FRC report no. 4. Washington, D.C.
- Federal Radiation Council. 1964a. *Background material for the development of radiation protection standards*. FRC report no. 5, July 1964. Washington, D.C.
- Federal Radiation Council. 1964b. *Revised fallout estimates for 1964-1965 and verification of the 1963 predictions*. FRC report no. 6, October 1964. Washington, D.C.
- Federal Radiation Council. 1965. *Background material for the development of radiation protection standards. Protective action guides for strontium-89, strontium-90, and cesium-137*. FRC report no. 7, May 1965. Washington, D.C.
- Federal Register. 1978. Accidental radioactive contamination of human and animal feeds and potassium iodide as a thyroid-blocking agent in a radiation emergency. *Federal Register*, pt. VII, December 15, 1978, pp. 58790-58800, Washington, D.C.
- Federation of American Societies for Experimental Biology. 1963. Fallout, food, and man. *Fed. Proc.*, 22(6) part 1:1389, November-December 1963. Proceedings of a symposium at the 47th annual meeting of the Federation of American Societies for Experimental Biology held in Atlantic City, April 20, 1963.
- Folsom, T. R. and D. R. Young. 1965. Silver-110m and cobalt-60 in oceanic and coastal organisms. *Nature* 206:803-6.
- FRC. See Federal Radiation Council.
- Furchner, J. E., J. S. Wilson, and C. R. Richmond. 1975. Cesium-137 activity in a normal New Mexico population: 1956-1973. *Health Phys.* 29:902. [Also annual progress reports from Los Alamos.]
- Garner, R. J. 1960. An assessment of the quantities of fission products likely to be found in milk in the event of aerial contamination of agricultural land. *Nature* 186:1063-64.
- George, L. A. Jr., P. L. Hackett, and L. K. Bustad. 1957. Triple radiation assault on debilitated lambs. In *Biology research annual report 1956*, HW-47500, pp. 115-23. Richland, Wash.: Hanford Atomic Products Operation.
- Glass, B. 1957. The genetic hazards of nuclear radiations. *Science* 126:241-46.
- Glasstone, S. and P. J. Dolan. 1977. *The effects of nuclear weapons*, 3d ed. Washington, D.C.: U.S. Department of Defense and U.S. Department of Energy.
- Gofman, J. W. 1981. *Radiation and health*, p. 908. San Francisco: Sierra Club Books.
- Greenhouse, N. A. and R. P. Miltenberger. 1977. *External radiation survey and dose predictions for Rongelap, Utirik, Rongerik, Ailuk, and Wotje Atolls*. BNL-50797. Upton, N.Y.: Brookhaven National Laboratory.
- Greenhouse, N. A., R. P. Miltenberger, and F. T. Cua. 1977. *Radiological analyses of Marshall Islands environmental samples. 1974-1976*. BNL-50796. Upton, N.Y.: Brookhaven National Laboratory.

- Greenhouse, N. A., R. P. Miltenberger, and E. T. Lessard. 1979. *External exposure measurements at Bikini Atoll*. BNL-51003. Upton, N.Y.: Brookhaven National Laboratory.
- Greenhouse, N. A., R. P. Miltenberger, and E. T. Lessard. 1980. Dosimetric results for the Bikini population. *Health Phys.* 38:846-51.
- Greenwald, P. 1969. Letter to James N. Yamczaki, UCLA Department of Pediatrics, responding to request from him for information on the New York State data, April 30, 1969.
- Gudiksen, P. H. and O. D. T. Lynch, Jr. 1975. Radioactivity levels in Eniwetok soil. *Health Phys.* 29:17-25.
- Hacker, B. C. undated. *Elements of controversy: A history of radiation safety in the nuclear weapons testing program*. [To be published under DOE auspices from Reynolds Electrical and Engineering Co., Las Vegas; first volume published in 1987. See footnote (b) on p. 883.]
- Hacker, B. C. 1987. *The dragon's tail: Radiation safety in the Manhattan Project, 1942-1946*. Berkeley, Calif.: Univ. of Calif. Press.
- Hakanson, T. E. and L. J. Johnson. 1974. Distribution of environmental plutonium in the Trinity Site ecosystem after 27 years. In *Proceedings of the 3d international congress of the International Radiation Protection Association*, ed. W. S. Snyder, CONF-730907-P1, pp. 242-47. Held in Washington, D.C., September 9-14, 1973. Oak Ridge, Tenn.: Technical Information Center.
- Hakanson, T. E. and J. W. Nyhan. 1980. Ecological relationships of plutonium in south-west ecosystems. In Hanson 1980, pp. 403-19.
- Hanson, W. C., ed. 1980. *Transuranic elements in the environment*. DOE/TIC-22800. Washington, D.C.: U.S. Department of Energy, Technical Information Center.
- Harley, J. H. 1969. Comments on fallout correlations made by Dr. Ernest Sternglass. In *Fallout program quarterly summary report*, HASL-214, vol. 1, pp. 1-2-I-7. New York: Health and Safety Laboratory.
- Harvey, R. L. 1952. *Maximum allowable concentrations of fission products in the air as a function of exposure time and time after detonation (continued)*. Interim report. U.S. Army Chemical Corps, CRLIR 81, Project 412-10-002. [This is a sequel to report CRLIR 64, which evaluated ^{90}Sr hazard.]
- Held, E. E. 1963. Qualitative distribution of radionuclides at Rongelap Atoll. In *Radioecology*, eds. V. Schultz and A. W. Klement, Jr., pp. 167-69. Proceedings of the 1st national symposium on radioecology held at Colo. State Univ., September 10-15, 1961. New York: Reinhold Publishing Co.; Washington, D.C.: American Institute of Biological Sciences.
- Held, E. E. 1971. Fallout radionuclides in Pacific Ocean tuna. In *Radionuclides in ecosystems*, ed. D. J. Nelson, CONF-710501-P2, pp. 689-93. Proceedings of the 3d national symposium on radioecology held in Oak Ridge, Tenn., May 10-12, 1971. Oak Ridge, Tenn.: Oak Ridge National Laboratories.
- Hewlett, R. G. and F. Duncan. 1969. *Atomic shield 1947/1952*. Vol. 2 of *A history of the United States Atomic Energy Commission*. University Park, Pa.: Penn State Univ. Press.
- Hines, N. O. 1962. *Proving ground: An account of the radiobiological studies in the Pacific, 1946-1961*. Seattle, Wash.: Univ. of Wash. Press.
- H.L.D. 1969. Scientist grabs the spotlight. Editorial in *Sci. Res.*, October 13, 1969.
- Hoffman, D. A., C. W. Harlow, and M. J. Tully. 1981. *A feasibility study of the biological effects of fallout on people in Utah, Nevada, and Arizona*. HHS pub. FDA-818151. Washington, D.C.: Bureau of Radiological Health, Food and Drug Administration.
- Holden, C. 1980. House report nails AEC for sheep deaths. *Science* 209:1097.
- Hull, A. P. and F. J. Shore. 1971. *Standards, statistics, and Sternglass: Guilt by association*. Paper presented at the 6th annual Health Physics Society topical symposium, held in Richland, Wash., November 1971. BNL-16255. Upton, N.Y.: Brookhaven National Laboratory.
- Hull, A. P. and F. J. Shore. 1972. *Sternglass: A case history*. BNL-16613. Upton, N.Y.: Brookhaven National Laboratory.
- ICRP. See International Commission on Radiological Protection.

- International Commission on Radiological Protection. 1965a. *Principles of environmental monitoring related to the handling of radioactive materials*. ICRP publ. 7. Oxford-London-New York: Pergamon Press.
- International Commission on Radiological Protection. 1965b. *Recommendations of the International Commission on Radiological Protection*. (Adopted September 17, 1965.) ICRP publ. 9. Oxford-London-New York: Pergamon Press.
- International Commission on Radiological Protection. 1979. *Radionuclide release into the environment: Assessment of doses to man*. ICRP publ. 29, annals of the ICRP 2, vol. 2, no. 2. New York-London: Pergamon Press.
- Izawa, M., H. Tsubota, and T. Nagai. 1961. Strontium-90 and cesium-137 in fallout deposits and implications of their ratio. *Radiat. Res.* 2:29-41.
- Jackson, W. B. and M. L. Carpenter. 1969. Radioisotope cycling in terrestrial communities at Eniwetok Atoll. In *Symposium on radioecology*, eds. D. J. Nelson and E. C. Evans, CONF-670503, pp. 644-51. Proceedings of the 2d national symposium on radioecology held in Ann Arbor, Mich., May 15-17, 1967. Springfield, Va.: National Technical Information Service.
- Japan Society for the Promotion of Science. 1956. *Research in the effects and influences of the nuclear bomb test explosives*. [General background to a series of reports by this title.]
- Johnson, W. S., Sr. and M. W. Carter. 1984. Irene H. Allen et al. vs. United States of America. A legal challenge to early radiation protection practices. In *Radiation—Risk—Protection*, eds. A. Kaul, R. Neider, J. Peňsko; F-E. Stieve, and H. Brunner, Compacts vol. 3, pp. 1269-72. Proceedings of the 6th international congress of the International Radiation Protection Association held in Berlin, May 7-12, 1984.
- Klauber, M. R. 1980. Lecture at Univ. of Calif., San Diego Medical School, January 28, 1980.
- Klement, A. W., Jr., ed. 1965. *Radioactive fallout from nuclear weapons tests*, CONF-765. Proceedings of the 2d conference held at Germantown, Md., November 3-6, 1964. Springfield, Va.: National Technical Information Service.
- Knapp, H. A. 1963. *Iodine-131 in fresh milk and human thyroids following a single deposition of nuclear test fallout*. Prepared for the U.S. Congressional hearings on fallout, radiation standards and countermeasures, June 1, 1963, pt. 2; August 1963, pp. 915-1075; plus ad hoc committee review, pp. 1076-78.
- Knapp, H. A. 1979. *Sheep deaths in Utah and Nevada following the 1953 Nevada tests*. Prepared for the Senate Subcommittee on Health and Scientific Research, the Senate Committee on the Judiciary, the House Subcommittee on Oversight and Investigations, and the Governor of Utah, August 1, 1979, with errata dated August 15, 1979. [Contains many appendices that include letters from various participating veterinarians, etc.]
- Kohn, H. I. and N. A. Dreyer. [with appendix by J. H. Harley]. 1982. *The radiation-induced risk of resettling Bikini Atoll*. Chestnut Hill, Mass.: Epidemiology Resources, Inc.
- Koranda, J. J., L. R. Anspaugh, and Y. C. Ng. 1982. Reconstruction of radiation doses to sheep in Penoyer Valley, NV, exposed to fallout from Shot Nancy in 1953. *Health Phys.* 43:105-6.
- Koranda, J. J. and J. R. Martin. 1971. Gamma-emitting radionuclides in Alaskan environments: 1967-1970. In *Radionuclides in ecosystems*, ed. D. J. Nelson, CONF-710501-P1, pp. 81-107. Proceedings at the 3d national symposium on radioecology held in Oak Ridge, Tenn., May 10-12, 1971. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Koranda, J. J., J. R. Martin, S. E. Thompson, Jr., M. L. Stuart, D. R. McIntyre, and G. Potter. 1973. Terrestrial biota survey. In *Eniwetok radiological survey*, NVO-140; vol. 1, pp. 225-348. Las Vegas: U.S. Atomic Energy Commission.
- Kulp, J. L., W. R. Eckelmann, and A. R. Schulert. 1957. Strontium-90 in man. *Science* 125:219-25.
- Kumatori, T. 1975. A summary of findings over the 20 year period on the Japanese fishermen exposed to fallout in 1954, pp. 89-93. Appendix 3 in Conard et al. 1975.

- Lade, J. H.: 1964. More on the 1953 fallout in Troy. *Science* 143:994-95.
- Land, C. E.: 1979. The hazards of fallout or of epidemiologic research? *N. Eng. J. Med.* 300:431-32.
- Land, C. E., F. W. McKay, and S. G. Machado.: 1984. Childhood leukemia and fallout from the Nevada nuclear tests. *Science* 223:139-44.
- Langham, W. H.: 1958. Potential hazard of world-wide Sr^{90} fallout from nuclear weapons testing. *Health Phys.* 1:105-24.
- Langham, W. H.: 1960. Radioisotopes—absorption and methods of elimination: Relative significance of portals of entry. In *Radioisotopes in the biosphere*, eds. R. S. Caldecott and L. A. Snyder, pp. 489-513. Proceedings of a symposium held in Minneapolis, October 19-23, 1959. Minneapolis: Univ. of Minn.; Center for Continuation Study.
- Langham, W. H. and E. C. Anderson.: 1958. *Potential hazard of world-wide Sr^{90} fallout from weapons testing*. Los Alamos Scientific Laboratory. [Seen in manuscript form. See also: Entry of radioactive fallout into biosphere and man: *Bull. Swedish Acad. Med. Sci.* 14:434-78.]
- Langham, W. H. and E. C. Anderson.: 1959. Cs^{137} biospheric contamination from nuclear weapons tests. *Health Phys.* 2:30-48.
- Lapp, R.: 1956. *Atoms and people*, ch. 7. New York: Harper Brothers.
- Larsen, P. R., R. A. Conard, K. Knudsen, J. Robbins, J. Wolff, J. E. Rall, and B. Dobyns.: 1978. Thyroid hypofunction appearing as a delayed manifestation of accidental exposure to radioactive fall-out in a Marshallëse population. In *Late biological effects of ionizing radiation*, STI/PUB/489, vol. 1, pp. 101-15. Proceedings of a symposium held in Vienna, March 13-17, 1978. Vienna: International Atomic Energy Agency.
- Larson, K. H.: 1963. Continental close-in fallout: Its history, measurement and characteristics. In *Radioecology*, eds. V. Schultz and A. W. Klement, Jr., pp. 19-25. Proceedings of the 1st national symposium on radioecology held at Colo. State Univ., September 10-15, 1961. New York: Reinhold Publishing Co.; Washington, D.C.: American Institute of Biological Sciences.
- Larson, K. H.: 1979. Taped interview at Seattle, Wash., June 1, 1979. Also undated report: *Continental close-in fallout: Its history, measurement, and characteristics*. A report of Dames and Moore, Seattle, Wash., by K. H. Larson.
- Larson, K. H. et al.: 1951a. *Alpha activity due to the 1945 atomic bomb detonation at Trinity, Alamogordo, New Mexico*. UCLA-108. Washington, D.C.: U.S. Atomic Energy Commission.
- Larson, K. H. et al.: 1951b. *The 1949 and 1950 radiological soil survey of fission product contamination and some soil-plant interrelationships of areas in New Mexico affected by the first atomic bomb detonation*. UCLA-140. Washington, D.C.: U.S. Atomic Energy Commission.
- Larson, K. H. et al.: 1952. *Field observations and preliminary field data obtained by the UCLA survey group on Operation Jangle, November, 1951*. UCLA-182. Washington, D.C.: U.S. Atomic Energy Commission.
- Larson, K. H., J. W. Neel, and associates.: 1960. *Summary statement of findings related to the distribution, characteristics, and biological availability of fallout debris originating from testing programs at the Nevada Test Site*. UCLA-438. Washington, D.C.: U.S. Atomic Energy Commission.
- Larson K. H., J. W. Neel, H. A. Hawthorne, H. M. Mork, R. H. Bowland, L. Baurmash, R. G. Lindberg, J. H. Olafson, and B. W. Kowalewsky.: 1966. *Distribution, characteristics, and biotic availability of fallout, Operation Plumbbob*. Projects 37.1, 37.2; 37.2a; 37.3 and 37.6 of the Civil Effects Test Group: WT-1488, July 26, 1966. Los Angeles: UCLA-Laboratory of Nuclear Medicine and Radiation Biology.
- Lawrence, W. L.: 1959. *Men and atoms—The discovery, the uses, and the future of atomic energy*. [Especially chapters 15 and 16: New York: Simon and Schuster.]
- Lee, H. et al.: 1983. *Organ doses from radionuclide intake by nuclear test personnel, 1945-1962*. Summary of final report to Nuclear Defense Agency from Advanced Research and Applications Corporation, Sunnyvale, Calif., September 29, 1980 to April 15, 1983.

- Leitch, J. L. 1951. *Summary of radiological findings in animals from the biological surveys 1947, 1948, 1949, and 1950*. UCLA-111. Washington, D.C.: U.S. Atomic Energy Commission.
- Lenihan, J. M. A., J. F. Loutit, and J. H. Martin, eds. 1967. *Strontium metabolism*. Proceedings of an international symposium held in Chapel Cross, Glasgow and Strontian, Scotland, May 5-7, 1966. London-New York: Academic Press.
- Lessard, E. T., N. A. Greenhouse, and R. P. Miltenberger. 1980. *A reconstruction of chronic dose equivalents for Rongelap and Utiirik residents—1954 to 1980*. BNL-51257. Upton, N.Y.: Brookhaven National Laboratory.
- Lessard, E. T., R. P. Miltenberger, and S. H. Cohn. 1980. *Internal exposure from Cs-137, Zn-65, Sr-90, Fe-55, and Pu-239 in Marshall Islands residents*. Upton, N.Y.: Brookhaven National Laboratory.
- Lessard, E. T., R. P. Miltenberger, and N. A. Greenhouse. 1980. Dietary radioactivity intake from bioassay data: A model applied to ^{137}Cs intake by Bikini Island residents. *Health Phys.* 39:177-83.
- Lessard, E., R. P. Miltenberger, R. A. Conard, S. V. Musolino, J. R. Naidu, R. Moorthy, and C. J. Schopfer. 1985. *Thyroid absorbed dose for people at Rongelap, Utiirik and Sifo on March 1, 1954*. BNL-51882. Upton, N.Y.: Brookhaven National Laboratory, Safety and Environmental Protection Division.
- Lewis, J. T., L. W. Grossman, J. G. Kereiakes, and E. L. Saenger. 1976. Cesium-137 body burdens and half-life in a group of adult males in Cincinnati, Ohio. *Health Phys.* 30:315-18.
- Libby, W. F. 1956a. Current research findings on radioactive fallout. *Proc. Nat. Acad. Sci. USA* 42:945-62.
- Libby, W. F. 1956b. Radioactive fallout and radioactive strontium. *Science* 123:657-60.
- Libby, W. F. 1956c. Radioactive strontium fallout. *Proc. Nat. Acad. Sci. USA* 42:365-90.
- Lindberg, R. G. et al. 1954. *Environmental and biological fate of fallout from nuclear detonations in areas adjacent to the Nevada Proving Grounds*. Project 27.2. Operation Upshot Knothole report WT-312.
- Lindberg, R. G., E. M. Romney, J. H. Olafson, and K. H. Larson. 1959. *Factors influencing the biological fate and persistence of radioactive fall-out*. [Operation Teapot, February/May 1955. Project 37.1 of Civil Effects.] Test Group report WT-1177. Oak Ridge, Tenn.: Technical Information Center.
- Lindop, P. J. and J. Rotblat. 1969. Strontium-90 and infant mortality. *Nature* 224:1257-60.
- List, R. J. 1956. *Radioactive fallout in North America from Operation Teapot*. NYO-4696 (Del). Washington, D.C.: U.S. Atomic Energy Commission.
- Lloyd, R. D. and J. Rundo. 1976. Half-life terminology for ^{137}Cs in humans. *Health Phys.* 31:527-28.
- Loutit, J. F. 1967. Strontium-90 from fallout in human bone. In Lenihan, Loutit, and Martin 1967, pp. 41-45.
- Loutit, J. F. 1969. Strontium in man. In *Environmental contamination by radioactive materials*, pp. 27-33. Proceedings of a symposium held in Vienna, March 24-28, 1969. Vienna: International Atomic Energy Agency.
- Lowe, C. H., Jr. 1947. *Trinity survey program, August 1947—herpeto fauna group*. Classified AEC report dated November 17, 1947, declassified February 29, 1972.
- Lowman, F. 1955. Abstract of oral report from an AEC meeting held May 19, 1955. [Quoted by Hines from files of Univ. of Wash. Applied Fisheries Laboratory.]
- Lowman, F. G. 1963. Radionuclides in plankton and tuna from the central Pacific. In *Radioecology*, eds. V. Schultz and A. W. Klement, Jr., pp. 145-49. Proceedings of the 1st national symposium on radioecology held at Colo. State Univ., September 10-15, 1961. New York: Reinhold Publishing Co.; Washington, D.C.: American Institute of Biological Sciences.
- Lüning, K. G., H. Frölen, A. Nelson, and C. Rönnbäck. 1963a. Genetic effects of strontium-90 injected into male mice. *Nature* 197:304-5.
- Lüning, K. G., H. Frölen, A. Nelson, and C. Rönnbäck. 1963b. Genetic effects of strontium-90 on immature germ cells in mice. *Nature*, 199:303-4.

- Lyon, J. L., M. R. Klauber, J. W. Gardner, and K. S. Udall. 1979. Childhood leukemias associated with fallout from nuclear testing. *N. Eng. J. Med.* 300:397-402.
- Machta, L. 1963. Meteorological processes in the transport of weapon radioiodine. *Health Phys.* 9:1123-32.
- Machta, L., R. J. List, and L. F. Hubert. 1956. World-wide travel of atomic debris. *Science* 124:474-77.
- Marshall, E. 1985. GAO finds errors in A-bomb test data. *Science* 230:1361.
- Martin, J. R. and J. J. Koranda. 1971. Recent measurements of cesium-137 residence time in Alaskan vegetation. In *Radionuclides in ecosystems*, ed. D. J. Nelson, CONF-710510-P1, pp. 108-15. Proceedings of the 3rd national symposium on radioecology held in Oak Ridge, Tenn., May 10-12, 1971. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Marx, J. L. 1979. Low-level radiation: Just how bad is it? *Science* 204:160-64.
- Mattoni, R. H. 1947. *Trinity survey program, August 1947—Entomology group*. Classified AEC report dated November 17, 1947, declassified February 29, 1972.
- Maxon, H. 1983. Personal communication concerning data being prepared for an NCRP report on thyroid risk.
- Mays, C. W. 1963. *Fallout, radiation standards and countermeasures*, 536-63. Testimony in Congressional hearings, 88th Cong., pt. 2, August 1963.
- McCone, J. A. 1959. *Fallout research and organization*. Hearings before the Joint Committee on Atomic Energy, Appendix K, vol. 3, March 24, 1959.
- Medical Research Council. 1956. *The hazards to man from nuclear and allied radiations*. First report to the MRC (U.K.) by a Wideherder Committee. Her Majesty's Stationery Office (Cmd. 9780), June 1956.
- Medical Research Council. 1960. *The hazards to man from nuclear and allied radiations*. Second report to the MRC (U.K.) by a Wideherder Committee. Her Majesty's Stationery Office (Cmd. 1225), December 1960.
- Meinke, W. W. 1951. Observations on radioactive snows at Ann Arbor, Michigan. *Science* 113:545-46.
- Micronesia. 1973. *A report on the people of Rongelap and Utirik, relative to medical aspects of the March 1, 1954 incident, injury, examination, and treatment*. Hearings before the Special Joint Committee Concerning Rongelap and Utirik Atolls (Public Law no. 4C-33) to the 5th Cong. of Micronesia. Senator Olympio T. Borja, chairman, February 1973.
- Miettinen, J. K. 1969. The present situation and recent developments in the accumulation of ^{137}Cs , ^{90}Sr and ^{55}Fe in arctic foodchains. In *Environmental contamination by radioactive materials*, pp. 145-51. Proceedings of a symposium held in Vienna, March 24-28, 1969. Vienna: International Atomic Energy Agency.
- Miltenberger, R. P., N. A. Greenhouse, and E. T. Lessard. 1980. Whole body counting results from 1974 to 1979 for Bikini Island residents. *Health Phys.* 39:395-407.
- Miltenberger, R. P., E. T. Lessard, and S. V. Musoline with many contributors. 1983. *Body burdens and dose assessment for Bikini Island residents*, draft report. Upton, N.Y.: Brookhaven National Laboratory.
- Moore, W., P. D. Lambert, and W. A. Mills. 1964. ^{131}I in bovine thyroids following atmospheric fallout from nuclear testing September 1961-January 1962. *Health Phys.* 10:61-64.
- Morley, F. and P. M. Bryant. 1969. Basic and derived radiological protection standards for the evaluation of environmental contamination. In *Environmental contamination by radioactive materials*, pp. 255-72. Proceedings of a symposium held in Vienna, March 24-28, 1969. Vienna: International Atomic Energy Agency.
- MRC. See Medical Research Council.
- Naidu, J. R., N. A. Greenhouse, G. Knight, and E. C. Craighead. 1980. *Marshall Islands: A study of diet and living patterns*. BNL-51313. Upton, N. Y. Brookhaven National Laboratory.
- NAS-NRC. See National Academy of Sciences-National Research Council.
- National Academy of Sciences. 1973. *Radionuclides in foods*. Report of the Committee on Food Protection, Food and Nutrition Board, Washington, D.C.

- National Academy of Sciences-National Research Council. 1956, 1961 and 1963. *The Biological effects of atomic radiation*. [A series of reports including a summary of, as separate reports, genetic effects, pathologic effects (pub. 452); with subcommittees on hematological effects (pub. 875); internal emitters (pub. 833); radioactive particles in the respiratory tract (pub. 848) and permanent and delayed effects of external sources (pub. 848); also meteorological aspects; oceanography and fisheries (pub. 551); agriculture and food supplies; soils and plants (pub. 1092); and dispersal of radioactive wastes (pub. 519). All available from the NAS-NRC, Washington, D.C., and reproduced in part in the 1957 Congressional hearings.]
- National Academy of Sciences-National Research Council. 1960. *Meteorological aspects of the effects of atomic radiation*. Washington, D.C.
- National Academy of Sciences-National Research Council. 1964. *Implications to man of irradiation by internally deposited strontium-89, strontium-90 and cesium-137*. A report of an advisory committee of the Division of Medical Sciences to the Federal Radiation Council, Washington, D.C.
- National Council on Radiation Protection and Measurements. 1971. *Basic radiation protection criteria*. NCRP report no. 39. Washington, D.C.
- National Council on Radiation Protection and Measurements. 1987. *Genetic effects from internally deposited radionuclides*. NCRP report no. 89. Bethesda, Md.
- Navy Department. 1947. Bikini scientific resurvey. Press release no. 10, July 15, 1947. [Quoted by Hines 1962.]
- NCRP. See National Council on Radiation Protection and Measurements.
- Neel, J. W. and K. H. Larson. 1963. Biological availability of strontium-90 to small native animals in fallout patterns from the Nevada Test Site. In *Radioecology*, eds. V. Schultz and A. W. Klement, Jr., pp. 45-49. Proceedings of the 1st national symposium on radioecology held at Colo. State Univ., September 10-15, 1961. New York: Reinhold Publishing Co.; Washington, D.C.: American Institute of Biological Sciences.
- Nevada Operations Office, U.S. Department of Energy. 1982. *Announced United States nuclear tests—July 1945 through December, 1981*. NVO-209 (Rev. 2), p. 68. [In cooperation with Los Alamos National Laboratory, Lawrence Livermore National Laboratory, and Sandia National Laboratories.]
- Newcombe, H. B. 1957. Magnitude of biological hazard from strontium-90. *Science* 126:549-51.
- Noshkin, V. E. 1980. Transuranium radionuclides in components of the benthic environment of Enewetak Atoll. In Hanson 1980, pp. 478-601. Washington, D.C.: Department of Energy, Technical Information Center. [Also UCRL-80587, February 1978.]
- Noshkin, V. E., R. J. Eagle, and K. M. Wong. 1976. Plutonium levels in Kwajalein Lagoon. *Nature* 262:745-48.
- Noshkin, V. E., K. M. Wong, and R. J. Eagle. 1979. Plutonium concentrations in fish and seawater from Kwajalein Atoll. *Health Phys.* 37:549-56.
- Noshkin, V. E., R. J. Eagle, K. M. Wong, T. A. Jokela, and W. L. Robison. 1981. *Radionuclide concentrations and dose assessment of cistern water and groundwater at the Marshall Islands*. UCRL-52853, pt. 2. Livermore, Calif.: Lawrence Livermore Laboratory.
- Noshkin, V. E., W. L. Robison, K. M. Wong, and R. J. Eagle. 1977. *Evaluation of the radiological quality of the water on Bikini and Eneu Islands in 1975: Dose assessment based on initial sampling*. UCRL-51879, pt. 4. Livermore, Calif.: Lawrence Livermore Laboratory.
- Noshkin, V. E., K. M. Wong, R. J. Eagle, and C. Gatroutsis. 1975. Transuranics and other radionuclides in Bikini Lagoon: Concentration data retrieved from aged coral sections. *Limnol. Oceanogr.* 20:729-42.
- NRC. See Nuclear Regulatory Commission.
- Nuclear Regulatory Commission. 1977. Letter from R. Muller, Advisory Committee on Reactor Safeguards of the NRC to chairman and members of the Environmental Subcommittee forwarding the FDA proposed guide for PAGs to replace the FRC guides. Letter dated January 14, 1977; letter from FDA dated December 7, 1976.
- NVO. See Nevada Operations Office, U.S. Department of Energy.

- Nyhan, J. W., F. R. Miera, Jr., and R. E. Neher. 1976. Distribution of plutonium in Trinity soils after 28 years. *J. Environ. Qual.* 5:431-37.
- Okabayashi, H. 1979. Distribution of experimentally inhaled plutonium in rats and fallout plutonium in human organs. In *Biological implications of radionuclides released from nuclear industries*, STI/PUB/522, vol. 1, pp. 371-83. Proceedings of a symposium held in Vienna, March 26-30, 1979. Vienna: International Atomic Energy Agency.
- Okajima, S., K. Takeshita, S. Antoku, T. Shiomi, W. J. Russell, S. Fujita, H. Yoshinaga, S. Neriishi, S. Kawamoto, and T. Norimura. 1978. Radioactive fallout effects of the Nagasaki atomic bomb. *Health Phys.* 34:621-33.
- Olafson, J. H. et al. 1957. *Distribution of plutonium in the soils of central and north-eastern New Mexico, as a result of the atomic bomb test of July 16, 1945*. UCLA-406. Washington, D.C.: U.S. Atomic Energy Commission.
- Olafson, J., J. Neel, J. Speigle, and R. H. Wilson. 1953. *Preliminary study of off-site airborne radioactive materials, Nevada Proving Grounds. I. Fallout originating from Snapper 6, 7, and 8 at distances of 10 to 50 miles from ground zero*. UCLA-243. Washington, D.C.: U.S. Atomic Energy Commission.
- Overstreet, R., L. Jacobson, and K. Larson. 1947. *Trinity survey program, August 1947—soils section*. Classified AEC report dated November 17, 1947, declassified February 29, 1972.
- Overstreet, R. et al. 1947. *Alamogordo report of 1947 survey*. UCLA-22. Washington, D.C.: U.S. Atomic Energy Commission.
- Pauling, L. 1958. Genetic and somatic effects of carbon-14. *Science* 128:1183-86.
- Pellerin, P., M. L. Remy, P. Ervet, and J. P. Moroni. 1967. Premier bilan de sept années de recherche sur les niveaux de la contamination du milieu ambiant et de la chaîne alimentaire par les retombées radioactives dans le territoire français. *Bull. de l'I.N.S.E.R.M.T.* 22:357-82.
- Pendleton, R. C., R. D. Lloyd, and C. W. Mays. 1963. Iodine-131 in Utah during July and August 1962. *Science* 141:640-42.
- Pendleton, R. C., J. J. Koranda, W. Wagner, P. Phelps, R. D. Lloyd, L. Anspaugh, and W. Chapman. 1971. Radioecological studies in Utah subsequent to the Baneberry Event. In *Radionuclides in ecosystems*, ed. D. J. Nelson, CONF-710501, vol. 1, pp. 150-69. Proceedings of the 3d national symposium on radioecology held in Oak Ridge, Tenn., May 10-12, 1971. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Pendleton, R. C., C. W. Mays, R. D. Lloyd, and A. L. Brooks. 1963. Differential accumulation of ¹³¹I from local fallout in people and milk. *Health Phys.* 9:1253-62.
- Perkins, R. W. and C. W. Thomas. 1980. Worldwide fallout. In Hanson 1980, pp. 53-82.
- Petrov, R. V. et al. 1966. *Radioactive fallout: Physics, biological effects and protective measures*, ed. A. I. Burnazyan. Translated from the Russian by Israel Program for Scientific Translations, Ltd., under agreement with the Atomic Energy Commission and National Science Foundation. Springfield, Va.: U.S. Department of Commerce.
- PHS. See Public Health Service.
- Public Health Service. 1964. *Environmental radiation surveillance*. Pub. no. 1224. Washington, D.C.
- Quesada, E. R. 1951. *Statement on results of Operation Greenhouse*. June 13, 1951. Washington, D.C.: U.S. Department of Defense, U.S. Atomic Energy Commission.
- Rallison, M. L., B. M. Dobyns, F. R. Keating, J. E. Rall, and F. H. Tyler. 1974. Thyroid disease in children: A survey of subjects potentially exposed to fallout radiation. *J. Am. Med. Assoc.* 56:457-63.
- Rallison, M. L., B. M. Dobyns, F. R. Keating, Jr., J. E. Rall, and F. H. Tyler. 1975. Thyroid nodularity in children. *J. Am. Med. Assoc.* 233:1069-72.
- Richardson, A. C. B. 1975. Environmental dose commitment. *Health Phys.* 29:353-54.
- Richmond, C. R. 1978. A comment on "Three decades of nuclear testing." *Health Phys.* 34:505.
- Richmond, C. R. and J. E. Furchner. 1967. Cesium-137 body burdens in man: January 1956 to December 1966. *Radiat. Res.* 32:538-49.

- Robison, W. L. 1973. Dose estimates for the marine food chain. In *Enewetok radiological survey*, NVO-140, vol. 1, pp. 526-41. Washington, D.C.: U.S. Atomic Energy Commission.
- Robison, W. L., W. A. Phillips, M. E. Mount, B. R. Clegg, and C. L. Conrado. 1980. Reassessment of the potential radiological doses for residents resettling Enewetak Atoll. UCRL-53066. Livermore, Calif.: Lawrence Livermore Laboratory.
- Roecklein, P. D., C. E. Smedley and R. E. Simpson. 1970. Strontium-90 and cesium-137 in total diet samples—A comparative study of data. *Radiol. Health Data Rep.* 11:47-64. Washington, D.C.: U.S. Public Health Service.
- Romney, E. M. et al. 1959. *An apparatus: A granular collector for sampling fall-out debris from nuclear detonations*. UCLA-432. Washington, D.C.: U.S. Atomic Energy Commission.
- Romney, E. M., R. G. Lindberg, J. E. Kinnear, and R. A. Wood. 1981. Persistence of ^{90}Sr and ^{137}Cs in fallout areas of southern Nevada and Utah, UCLA 12-1308. Prepared for Health Physics Division, Nevada Operations Office, U.S. Department of Energy. UCLA Laboratory of Biomedical and Environmental Sciences.
- Russell, R. S. and R. S. Bruce. 1969. Environmental contamination with fall-out from nuclear weapons: A review. In *Environmental contamination by radioactive materials*, pp. 3-13. Proceedings of a symposium held in Vienna, March 24-28, 1969. Vienna, Austria: International Atomic Energy Agency.
- Sakanoue, M. and T. Tsuji. 1971. Plutonium content of soil at Nagasaki. *Nature* 234:92-93.
- Sasaki, M. S. and H. Miyata. 1968. Biological dosimetry in atomic bomb survivors. *Nature* 220:1189-93.
- Schell, W. R. 1975. Concentrations and physical-chemical states of ^{55}Fe in Bikini Atoll Lagoon. In *Radioecology and energy resources*, ed. C. E. Cushing, Jr., Ecological Society of America special publ. no. 1, pp. 271-76. Proceedings of the 4th national symposium on radioecology held at Oreg. State Univ., May 12-14, 1975. Stroudsburg, Pa.: Dowden, Hutchinson & Ross, Inc.
- Seaborg, G. T. 1963. Letter and attachment, Iodine-131 in fallout. In *U.S. Congressional hearings on fallout, radiation standards, and countermeasures*, pt. 2, pp. 1101-4.
- Seymour, A. H. 1963a. Gamma-emitting radionuclides in tuna samples from Tokyo Central Fish Market. UWFL-90. Washington, D.C.: U.S. Atomic Energy Commission.
- Seymour, A. H. 1963b. Radioactivity of marine organisms from Guam, Palau and the Gulf of Siam, 1958-1959. In *Radioecology*, eds. V. Schultz and A. W. Klement, Jr., pp. 151-57. Proceedings of the 1st national symposium on radioecology held at Colo. State Univ., September 10-15, 1961. New York: Reinhold Publishing Co.; Washington, D.C.: American Institute of Biological Sciences.
- Seymour, A. H. 1985. Personal interview, Seattle, Wash.
- Shaw, R. F. and A. P. Smith. 1970. Strontium-90 and infant mortality in Canada. *Nature* 228:667-69.
- Sherrod, R. 1954. The grim facts of the H-bomb accident. *Saturday Evening Post*, July 17, 1954.
- Shelton, A. V., R. H. Gaeke, W. R. Kennedy, K. H. Larson, K. M. Wagler, and O. R. Placak. 1959. Unpublished report. Test Manager's Committee to Establish Fallout Doses. [Available at Coordination and Information Center, REECO.]
- Shiraishi, Y. and R. Ichikawa. 1970. Fallout ^{90}Sr in beer. *Health Phys.* 19:443-44.
- Shleien, B. 1970. An evaluation of internal radiation exposure based on dose commitments from radionuclides in milk, food and air. *Health Phys.* 18:267-75.
- Shleien, B. 1981a. Comments on "The recommendations of the Bureau of Radiological Health on how to deal with fallout contamination are not sufficiently conservative," by C. Swick and K. Z. Morgan. *Health Phys.* 40:128.
- Shleien, B. 1981b. External radiation exposure to the offsite population from nuclear tests at the Nevada Test Site between 1951 and 1970. *Health Phys.* 41:243-54.
- Shukla, K. K., C. S. Dombrowski, and S. H. Cohn. 1973. Fallout ^{137}Cs levels in man over a 12 yr period. *Health Phys.* 24:555-57.
- Simpson, R. E., E. J. Baratta, and C. F. Jelinek. 1974. Radionuclides in foods: Monitoring program. *Radiat. Data Rep.* 15:647-56. Washington, D.C.: U.S. Environmental Protection Agency.

- Simpson, R. E., E. J. Baratta, and C. F. Jelinek. 1977. Radionuclides in foods. *J. Assoc. Off. Anal. Chem.* 60:1364-68.
- Smith, F., D. W. Boddy, and M. Goldman. 1952. *Biological injury from particle inhalation*. Operation Jangle, Project 2.7, report WT-396 (Del. 2). Declassified with deletions, September 25, 1959.
- Smith, R. J. 1982a. Atom bomb tests leave infamous legacy. *Science* 218:266-69.
- Smith, R. J. 1982b. Scientists implicated in atom test deception. *Science* 218: 545-47.
- Smith, R. J. 1983. Reagan reluctantly approves fallout study. *Science* 219:269.
- Smith, R. J. 1984. Judge says atom tests caused cancer. *Science* 224:853, 856.
- Smith, R. J. 1985. NRC finds few risks for atomic vets. *Science* 228:1409.
- Sowby, F. D. 1969. Setting dose limits for the public. In *Environmental contamination by radioactive materials*, pp. 215-19. Proceedings of a symposium held in Vienna, March 24-28, 1969. Vienna: International Atomic Energy Agency.
- Stannard, J. N. 1976. Summary and comments. In *Radiation and the lymphatic system*, ed. J. E. Ballou, CONF-740930, pp. 246-48. Proceedings of the 14th annual Hanford biology symposium held at Richland, Wash., September 30-October 2, 1974. Springfield, Va.: National Technical Information Service.
- Sternglass, E. J. 1963. Cancer: Relation of prenatal radiation to development of the disease in childhood. *Science* 140:1102-4.
- Sternglass, E. J. 1969a. Article in *Medical Tribune*, July 21, 1969.
- Sternglass, E. J. 1969b. Article in *Medical Tribune*, July 28, 1969.
- Sternglass, E. J. 1969c. Can the infants survive? *Bull. At. Sci.* 25:26.
- Sternglass, E. J. 1969d. Infant mortality and nuclear tests. *Bull. At. Sci.* 25:18-20.
- Sternglass, E. J. 1969e. The death of all children. *Esquire Magazine*, September 1969.
- Sternglass, E. J. 1972a. *Low-level radiation*. New York: Ballantine Books.
- Sternglass, E. J. 1972b. The relative health effects of medical and environmental radiation. Paper presented at the 14th annual meeting of the Association of Physicists in Medicine, held at Philadelphia, June 1972.
- Sternglass, E. J. 1976. The role of indirect radiation effects on cell membranes in the immune response. In *Radiation and the lymphatic system*, ed. J. E. Ballou, CONF-740930, pp. 185-91. Proceedings of the 14th annual Hanford biology symposium held in Richland, Wash., September 30-October 2, 1974. Springfield, Va.: National Technical Information Service.
- Strauss, L. L. 1962. *Men and decisions*. Garden City, N. Y.: Doubleday and Co.
- Suzuki, M. undated. The injuries caused by radiation fall-out from thermonuclear explosion test on Japanese fishermen. Personal communication.
- Suzuki, M. 1956. Medical consideration on radiation injury due to Bikini fallout. In *Research in the effects and influences of the nuclear bomb test explosions*, pt. 7. Committee for reports on research in the effect of radiation. Tokyo: Japan Society for the Promotion of Science.
- Swick, C. and K. Z. Morgan. 1980. The recommendations of the Bureau of Radiological Health, on how to deal with fallout contamination, are not sufficiently conservative. *Health Phys.* 38:432-33.
- Sztanyik, L. B. 1978. Late radiobiological effects of A-bombing in Japan. In *Late biological effects of ionizing radiation*, STI/PUB/489, vol. 1, pp. 61-70. Proceedings of a symposium held in Vienna, March 13-17, 1978. Vienna: International Atomic Energy Agency.
- Tamplin, A. R. and H. L. Fisher. 1966. *Estimation of dosage to thyroids of children in the U.S. from nuclear tests conducted in Nevada during 1952 through 1955*. UCRL-14707. Berkeley, Calif.: Lawrence Radiation Laboratory.
- Tamplin, A. R., Y. Ricker, and M. F. Longmate. 1969. *A criticism of the Sternglass article on fetal and infant mortality*. UCID-15506. Livermore, Calif.: Lawrence Livermore Laboratory.
- Taplin, G. V., O. M. Meredith, Jr., and H. Kade. 1955. *Evaluation of the acute inhalation hazard from radioactive fallout materials by analysis of results from field operations and controlled inhalation studies in the laboratory*. Operation Teapot, Project 37.3, preliminary report ITR-1172. Official use only. Washington, D.C.: U.S. Atomic Energy Commission, Technical Information Center.

- Taylor, L. S. and K. O. Sauer. 1984. Vignettes of early radiation workers. [Transcripts of a videotape series by the same name.] Rockville, Md.: U.S. Dept. of Health and Human Services, Food and Drug Administration Center for Devices and Radiological Health.
- Thomas, R. G., E. C. Anderson, and C. R. Richmond. 1978. ¹³⁷Cs whole-body content in a normal New Mexico population: 1957-1977. LA-UR 78-3211 (Revised).
- Tomkins, E. and M. L. Brown. 1969. *Evaluation of a possible causal relationship between fallout deposition of strontium-90 and infant and fetal mortality trends*. DBE 69-2. Rockville, Md.: U.S. Public Health Service, Bureau of Radiological Health.
- Toohy, R. E., J. Rundo, M. A. Essling, J. Y. Sha, and R. D. Oldham. 1981. Radioactivity measurements of former military personnel exposed to weapons debris. *Science* 213:767-68.
- Totter, J. R., M. R. Zelle, and H. Hollister. 1958. Hazard to man of carbon-14. *Science* 128:1490-95.
- Troitskaya, M. N., M. S. Ibatullin, B. Ya. Litver, A. A. Moiseyev, A. I. Nizhnikov, P. V. Ramzayev, and L. A. Teplyk. 1974. Analysis of geographical differences in the rate of purification of the chain lichens-reindeer-man from cesium-137. In *Proceedings of the 3d international congress of the International Radiation Protection Association*, ed. W. S. Snyder, CONF-730907-P1, pp. 266-71. [Text in Russian, abstract in English.] Held in Washington, D.C., September 9-14, 1973. Oak Ridge, Tenn.: Technical Information Center.
- Tullis, J. L. and S. Warren. 1947. Gross autopsy observations in the animals exposed at Bikini: A preliminary report. *J. Am. Med. Assoc.* 134:1155-58.
- United Nations Scientific Committee on the Effects of Atomic Radiation: 1958 et seq. UNSCEAR 1958, 13th sess., suppl. no. 17 (A/3838); 1962, 17th sess., suppl. no. 16 (A/5216); 1964, 19th sess., suppl. no. 14 (A/5814); 1966, 21st sess., suppl. no. 14 (A/6314); 1969, 24th sess., suppl. no. 13 (A/7613); 1972, vols. I & II, sales nos. E.72.IX.17 and 18 1977; 32d sess., suppl. no. 40 (A/32/40); 1982, 37th sess., suppl. no. 45 (A/37/45).
- UNSCEAR. See United Nations Scientific Committee on the Effects of Atomic Radiation.
- U.S. Congress. 1955. *Health and safety problems and weather effects associated with atomic explosions*. Hearings before the Joint Committee on Atomic Energy, 84th Cong., April 15, 1955.
- U.S. Congress. 1957. *The nature of radioactive fallout and its effects on man*. Hearings before the Joint Committee on Atomic Energy, 85th Cong., Special Subcommittee on Radiation. May 27, 28, 29 and June 3, 1957. Testimony of W. Selove, pp. 1292-96.
- U.S. Congress. 1959. *Fallout from nuclear weapons tests*. Hearings before the Joint Committee on Atomic Energy, 86th Cong., May 5-8, 1959. Several volumes and survey analysis, August 1959.
- U.S. Congress. 1962. *Radiation standards, including fall-out*. Hearings before the Joint Committee on Atomic Energy, 87th Cong., June 47, 1962.
- U.S. Congress. 1963. *Fallout, radiation standards, and countermeasures*. Hearings before the Joint Committee on Atomic Energy, Subcommittee on Research, Development, and Radiation, 88th Cong., June 3-6, August 20, 21, 22 and 27, 1963.
- U.S. Congress. 1980. *The forgotten guinea pigs*. A report on health effects of low-level radiation sustained as a result of the nuclear weapons testing program conducted by the United States Government. Hearings before the House Committee on Interstate and Foreign Commerce, 96th Cong., 2d. Sess. Committee Print 96-IFC53.
- Van Dilla, M. 1959. Los Alamos Scientific Laboratory, unpublished data quoted by Langham 1960.
- Van Middlesworth, L. 1954. Radioactivity in animal thyroids from various areas. *Nucleonics* 12(9):56-57.
- Van Middlesworth, L. 1956. Radioactivity in thyroid glands following nuclear weapons tests. *Science* 123:982-83.
- Van Rossem, A. J. 1947. *Trinity survey program, August 1947—ornithology group*. Classified AEC report dated November 17, 1947, declassified February 29, 1972. Washington, D.C.: U.S. Atomic Energy Commission.

- Visalli, F. I. and A. S. Goldin. 1963. Fallout I^{131} in children—*in vivo* measurements. *Health Phys.* 9:1271-77.
- Webb, J. H. 1949. The fogging of photographic film by radioactive contaminants in cardboard packaging materials. *Phys. Rev.* 76:375-80.
- Wegst, A. V., C. A. Pelletier, and G. H. Whipple. 1964. Detection and quantitation of fallout particles in a human lung. *Science* 143:957-59.
- Weiss, E. S., M. L. Rallison, W. T. London, and G. D. Carlyle Thompson. 1971. Thyroid nodularity in southwestern Utah school children exposed to fallout radiation. *Am. J. Public Health* 61:241-49.
- Weiss, H. V. 1956. Residual contamination of plants, animals, soil, and water of the Marshall Islands two years following Operation Castle fallout. In *The shorter-term biological hazards of a fallout field*, eds. G. M. Dunning and J. A. Hilcken, pp. 205-10. Proceedings of a symposium held December 12-14, 1956. Washington, D.C.: U.S. Atomic Energy Commission.
- Welander, A. D. 1969. Distribution of radionuclides in the environment of Eniwetok and Bikini Atolls, August 1964. In *Symposium on radioecology*, eds. D. J. Nelson and F. C. Evans, CONF-670503, pp. 346-54. Proceedings of the 2d national symposium on radioecology held in Ann Arbor, Mich., May 15-17, 1967. Springfield, Va.: National Technical Information Service.
- Wellman, H. N., G. J. Karuches, Hanson, G. R. Laurer, M. Eisenbud, Fooks. 1965. Iodine 131 in children's thyroids from environmental exposure. U.S. Public Health Service Environmental Health Series Report, PHS Publ. no. 999-R+1-14 (July 1965). Washington, D.C.: U.S. Government Printing Office.
- Wexler, H. L. Machta, D. H. Pack, and F. D. White. 1956. Atomic energy and meteorology. In *Proceedings of the international conference on the peaceful uses of atomic energy*, vol. 13, pp. 333-44. Held in Geneva, August 8-20, 1955. New York: United Nations.
- White, M. R. and H. B. Jones. 1956. Uptake of iodine- 131 in human and bovine thyroids following detonation of nuclear weapons. In *The shorter-term biological hazards of a fallout field*, eds. G. M. Dunning and J. A. Hilcken. Proceedings of a symposium held December 12-14, 1956. Washington, D.C.: U.S. Atomic Energy Commission.
- Wilson, D. W., Y. C. Ng, and W. L. Robison. 1975. Evaluation of plutonium at Enewetak Atoll. *Health Phys.* 29:599-611.
- Wolff, A. H. 1957. Radioactivity in animal thyroid glands. *Public Health Rep.* 72:1121-26.
- Wrenn, M. E. 1981a. A review of external radiation dose estimates offsite associated with nuclear testing at the Nevada test site and current research. In *Quantitative risk in standards setting*, pp. 179-92. Proceedings of the 16th annual meeting of the NCRP. Washington, D.C.: National Council on Radiation Protection and Measurements.
- Wrenn, M. E. 1981b. Testimony to the Senate Committee on labor and human resources regarding the radiation exposure compensation act of 1981. October 27, 1981.

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Capsule Chronology

- 1945** Alamogordo (Trinity) cattle go to Oak Ridge.
- July 1946** Results of Operation Crossroads generate need for laboratory devoted to such problems. Lead to organization of Naval Radiological Defense Laboratory (NRDL)^(a) at San Francisco.
- Aquatic biology of radionuclides gets boost for both laboratory and field studies.
- November 1946** NRDL begins work on small scale.
- 1947 et seq.** Work on mice by M. Finkel (Argonne) expands. Later includes special experiment on radiostrontium. Continues into 1970s.
- 1948** AEC lets contract with University of Tennessee Agricultural Research Laboratory, theoretically for further follow-up of Alamogordo cattle, but soon becomes much broader. Cyril Comar appointed as director. Staff includes Lengemann and Wasserman, Hood and Hansard. Called UT-AEC Farm.
- 1949** Nine projects already under way at UT-AEC.
- NRDL becomes more biomedical and expands.
- 1950** Utah project organized. Work not initially oriented toward fallout problems but expanded later to include them (details in chapter 8).
- 1950s et seq.** UCLA project concentrates on laboratory and glasshouse experiments relevant to fallout radionuclides.
- 1950s** Work starts at Berkeley on ^{90}Sr in rhesus monkey (Durbin).
- Studies at Hanford begin on uptake and translocation of fission products by plants; continues indefinitely and expands to transuranics.
- Hanford study of ^{90}Sr in miniature swine (Bustad, McClellan, and Kornberg).
- Hanford studies on passage of pairs of elements through soil and food chains (Kornberg and Thompson).
- Hanford studies on fallout radionuclides in fetal and juvenile mammal (Sikov and Mahlum).
- Comar et al. develop Observed Ratio (OR) approach to describe relative behavior of pairs of elements (UT-AEC). Used extensively to describe metabolism of fallout radionuclides. Sometimes carried too far. Discrimination processes and discrimination factors much emphasized.
- Laboratory work on diets confirms and extends findings from the field.
- 1956** University of California-Davis project organized primarily for feeding of radiostrontium to beagles, but other dimensions added.

(a) For abbreviations and acronyms, see Appendix D.

- 1957** Cyril Comar goes to Cornell University to establish Department of Physical Biology and radiobiology program, including effects as well as mineral metabolism.

Experimental work with plants indicates same basic behavior of isotopes as in animals (Romney et al., UCLA). Clear that much of the absorption of radionuclides by plants is foliar. Amplified by subsequent work in many other laboratories.

Chapters on laboratory experiments with marine organisms in NAS-NRC report on oceanography and fisheries (see chapter 11).

- 1958** Oak Ridge work becomes quite experimental.

Studies begin on radiostrontium behavior in man (Spencer et al.).

- 1959** PHS establishes regional radiological health facilities. The one at Las Vegas is especially involved in research stimulated by the problems of fallout (named Southwestern Radiological Health Laboratory—SWRHL). Work on radionuclides seen in fallout carried out also at Radionuclide Toxicity Laboratory in Robert A. Taft Center in Cincinnati. Later moved to Rockville, Maryland. Other regional laboratories are described in chapter 11.

- 1960** Minnesota symposium contains many reports on experimental work stimulated by the problems of fallout.

Successive generation plant work at UCLA indicates gradual changes in solubility of radionuclides (Romney et al., UCLA).

- 1960s.** UT-AEC work confirms in large animals most of the earlier findings in small animals concerning fallout radionuclides.

Brookhaven work shows real differences among responses of higher plants and animals to radiation.

Rochester work on strontium in monkeys and rats (Casarett and Tuttle), also renal clearance (Della Rosa, Smith, and Stannard) and life-span shortening (Blair).

Brookhaven whole-body counting facility brought to bear on many problems of radionuclides from fallout in man and animals (Cohn et al.).

Argonne National Laboratory experiments with cesium in dogs.

- 1961** Lovelace facility initiated. Centers on many inhalation problems (chapter 9) but uses radionuclides in fallout.

Much work on mechanisms of discrimination between elements.

Relation between nuclear volume and radiosensitivity of plants established (Sparrow, Brookhaven).

- 1963** An NAS-NRC BEAR report summarizes behavior of radionuclides from fallout in soils and plants.

Reports on tracer level studies of cesium in man (Spencer et al.).

- 1964** Reports of Los Alamos work on effects of various factors on behavior of fallout radionuclides.

- 1965** Book edited by Fowler (Los Alamos) has many reports of experimental work with fallout radionuclides.

Discrimination factors described for plants in different soils (Nishita, UCLA).

Much work on effects of diet and age on discrimination in animals and man (Comar et al., Cornell).

- 1966** Concluded that Alamogordo cattle possess normal breeding efficiency, but hyperkeratosis is evident (Brown, Bird et al., UT-AEC).

- 1967** Book, *Strontium Metabolism*, published in United Kingdom (Lenihan, Loutit, and Martin, eds.).

Stockholm Symposium on Radionuclide Concentration Processes (Åberg and Hungate, eds.). Contains review by Polikarpov on experimental work with aquatic forms. Also much work with plants.

Several laboratories develop whole-body counters for fish to investigate mobility of radionuclides.

- 1969** NRDL closed.

Laboratory studies of clam and quahog (Andrews and Warren; Rochester, Harvard).

Differences in metabolism as function of route of administration and other factors established for many radionuclides (McClellan and Jones).

Effects of strontium on farrowing performance of animals occur only at very high doses (Battelle, Lovelace).

- Late 1960s** UT-AEC Farm becomes Comparative Animal Research Laboratory (key staff—Brown, Bell, Miller, Mraz, Noonan, Reynolds, Spalding, Hansard).

- 1970** EPA takes over PHS-BRH regional laboratories. Programs continue.

- 1970s** Gradual shift from strontium, cesium, etc., to tritium, krypton, radium, and uranium from mill tailings.

- 1972** Strontium Symposium at University of California-Davis reviews large amount of experimental work stimulated by problems of fallout (Goldman and Bustad, eds.).

- 1976** Order of sensitivity of marine organisms described at IAEA symposium.

- 1977** NCRP report on experimental work with radiocesium over the previous decades.

- 1978** NCRP report summarizes experimental work on radiocerium.

- 1980** Much experimental work in book on transuranics edited by Hanson (see chapter 11).

- 1981** Review of experimental work on soils in issue of *Soil Science* (several laboratories).

1. The first part of the document is a letter from the President of the United States to the Congress, dated January 3, 1862.

2. The second part is a report from the Secretary of the Treasury, dated January 3, 1862.

3. The third part is a report from the Secretary of the Interior, dated January 3, 1862.

4. The fourth part is a report from the Secretary of the Navy, dated January 3, 1862.

5. The fifth part is a report from the Secretary of the War, dated January 3, 1862.

6. The sixth part is a report from the Secretary of the State, dated January 3, 1862.

7. The seventh part is a report from the Secretary of the Army, dated January 3, 1862.

8. The eighth part is a report from the Secretary of the Navy, dated January 3, 1862.

9. The ninth part is a report from the Secretary of the War, dated January 3, 1862.

10. The tenth part is a report from the Secretary of the State, dated January 3, 1862.

11. The eleventh part is a report from the Secretary of the Army, dated January 3, 1862.

12. The twelfth part is a report from the Secretary of the Navy, dated January 3, 1862.

13. The thirteenth part is a report from the Secretary of the War, dated January 3, 1862.

14. The fourteenth part is a report from the Secretary of the State, dated January 3, 1862.

15. The fifteenth part is a report from the Secretary of the Army, dated January 3, 1862.

16. The sixteenth part is a report from the Secretary of the Navy, dated January 3, 1862.

17. The seventeenth part is a report from the Secretary of the War, dated January 3, 1862.

18. The eighteenth part is a report from the Secretary of the State, dated January 3, 1862.

19. The nineteenth part is a report from the Secretary of the Army, dated January 3, 1862.

20. The twentieth part is a report from the Secretary of the Navy, dated January 3, 1862.

Chapter 13

Biomedical Research Stimulated by the Problems of Fallout

Overview

This chapter concerns scientific experiments. With some exceptions, the activities described in chapter 12 were centered on *observations*, e.g., finding the facts about the behavior and possible effects of the radionuclides from weapons testing in elements of the biosphere. There was no control over the variables, just measurements.

To understand the results obtained, to be able to make more satisfactory predictions, and to be able perhaps to take some measure of remedial action, experimental work under controlled conditions was deemed essential. While the laboratory work of the Manhattan District and its early post-World War II extensions (chapters 6, 7, and 8) and the classic studies with naturally occurring radioisotopes (chapters 1 to 4) provided a long start, there were many problems more or less specific to the fallout situation that mandated equally specific experimental approaches. It is these that we will undertake to review in these pages.

"Experimental" in the context of this chapter means both laboratory and field-type investigations. So long as the plan was to manipulate certain variables while keeping others constant in order to observe the behavior or effects of radionuclides characteristic of fallout, we will define it as "research." Obviously, our choice of whether or not the output of certain programs is to be regarded as "stimulated by the problems of fallout" has had to be somewhat arbitrary. Since the same radionuclides are of biomedical importance in many contexts, there is inevitably overlap between the types of work we considered in chapter 8, work we have considered in connection with nuclear reactors,^(a) around production sites (chapter 11), and the work described in this chapter. Nevertheless this does not prevent us from selecting out the research that we deem most pertinent to the subject at hand.

(a) Much of the research begun around the problems of fallout has continued, of course, around more general problems of environmental contamination, including that from nuclear reactors.

As alluded to in earlier chapters, there were laboratories that came into being primarily to attack the problems raised by fallout. We consider them and their work first. In addition, the established laboratories modified or expanded their programs in order to attack some of the problem areas defined in chapter 12. Some laboratories, e.g., the University of California at Davis, were engaged in a general attack on radionuclide toxicity and pharmacokinetics, but the timing of their organization and results puts them neatly within the purview of the present discussions. For this reason, we promised in chapter 8 to review details of their findings here. Some laboratories underwent only perturbations in their programs, not major changes in direction (e.g. Argonne National Laboratory, University of Rochester). Every laboratory in the world with capability and interest in work concerning radionuclides in the biosphere participated in some way in research or surveillance concerned with fallout. To these we can devote only minor attention, but pertinent reviews will be cited.

Financial support for these enterprises came primarily from governmental agencies. The early efforts were supported largely by the military, particularly the U.S. Navy. Funds from the military continued to play an important role through agencies such as the Armed Forces Special Weapons Project and its successor, the Defense Nuclear Agency.^(a)

The Atomic Energy Commission played a central role both financially and in the provision of facilities and personnel. This was continued under the Energy Research and Development Administration and the Department of Energy. The U.S. Public Health Service also played a substantial role in research as it did in surveillance. The Public Health Service programs were taken over by the Environmental Protection Agency on its inception in 1970.

I. New Laboratories

We will take up the organization, mission, and broad programs of those laboratories created around the problems of fallout in approximate chronological order of their founding and development. Most details of the research findings will be discussed under the several headings in sections III and IV, since we need to consider the results en masse.

A. The U.S. Naval Radiological Defense Laboratory

The *raison d'être* for this laboratory lay in the tons of highly contaminated sea water that showered down upon the assembled flotilla of warships in Test Baker of Operation Crossroads (chapter 12) on July 25, 1946. As the still-contaminated ships limped back to the continental United States from Bikini Atoll, test personnel, made grimly aware that fallout contamination could be serious business, even lethal, urged the establishment of a laboratory group to search for urgently needed countermeasures. Thus, as R. A. Hinnens stated (1957)^(b) "like Venus, NRDL was born in the foam of the sea."

(a) Biomedical problems were, of course, only a small fraction of their total investment.

(b) I am indebted to Dr. C. Sharp Cook, Department of Physics, University of Texas at El Paso, for making this and other scarce reference material available to me. Dr. Cook spent several years at the Naval Radiological Defense Laboratory (NRDL) heading the Nucleonics Division. Captain Hinnens was Commanding Officer of NRDL from 1953 to 1956. Also Dr. Burton Vaughan, Battelle, and Dr. William Kreager, retired, supplied notes and references.

The ships moved, sometimes with intermediate stops, to the San Francisco Naval Shipyard on Hunters Point in San Francisco Bay. The presence there of a large Naval facility, some temporary buildings left over from World War II, and the proximity of educational institutions that might act as sources of both ideas and personnel fostered the decision to develop a laboratory there. Biomedical problems were not paramount in the minds of the founders. Decontamination was the pervasive issue. However, it soon became apparent that there were huge gaps in our knowledge regarding the biological effects of moderate to large doses of whole-body radiation,^(a) particularly effects that might bear on the ability of military personnel to carry out their missions. Also, there was concern over problems of food and water contamination, what to do about the extremely "hot" fouling organisms that could turn the sides of a ship into extended radiation sources (chapter 12), and other quasi-biomedical problems. Thus, very soon the organizational plan called for close collaboration between physical and biological scientists. While the facility was developed under the Bureau of Ships of the U.S. Navy, it was planned that the Bureau of Medicine and Surgery would supply personnel and funds and utilize the facilities for studies of radiological hazards.

Obviously, the laboratory did not start with such cooperation in place. Indeed, the laboratory consisted initially of a few junior officers, a few Geiger counters, some scalars, mostly borrowed (Hinnens 1957), and the all-important coffee urn. This was in November 1946.

From this grew an organization that was eventually housed in a multimillion-dollar facility with four major scientific divisions, one of which was "Biological and Medical Sciences." The program of the laboratory as of 1959 (OPNAV Report 1959)^(b) was outlined as follows:

Current Program

In its growth and development the seven broad phases of the scientific program now cover:

1. Determination of the characteristics of harmful radiations and radioactive materials.
2. Study of atomic explosion phenomenology and weapons effects.
3. Study of hazards of nuclear radiations to personnel.
4. Development of instruments to detect, identify and measure radioactivity.
5. Development of countermeasures for removing radioactive contamination and for minimizing or preventing contamination.
6. Study of measures to minimize harmful effects of nuclear radiation on human beings.
7. Study of physical and biological effects of thermal radiations accompanying nuclear weapons detonations.

We saw in chapter 12 that personnel from NRDL had much to do with the Pacific tests, including study of the exposed Marshallese. This gave them first-hand experience that could influence their laboratory research and vice versa. As already noted (see also chapter 19), development of chelation therapy for

(a) Most of the emphasis for protection had been on occupational exposures or on the procedures used in radiation therapy and diagnostic radiology.

(b) I am indebted to Dr. Dean Allard, Navy Historian's Office, Navy Yard, Washington, D.C., for facilitating my review at that facility of eleven reports on the history of the NRDL and for preparing copies of unclassified excerpts. The 1959 report cited covers the period 1946-1958.

removal of deposited radionuclides was included in the early work of the NRDL biomedical program and constituted a clear interaction of field and laboratory.

In the chapter on inhalation toxicology (chapter 9), we met work, especially by Cohn and Gong, on inhalation of a fallout simulant by animals. In chapter 3, we saw that these same authors even took a foray into the problems of radon and radon daughters.^(a)

Much emphasis in the NRDL program went to external radiation sources, both ionizing and thermal. The cited summary report reviews the biomedical program of the time (1958) as follows:

Biological and Medical Sciences. This division is involved with problems of injury to personnel resulting from nuclear and thermal radiation. From the earliest days of the Laboratory, biologists and doctors of medicine have been studying the complex relationships between radiation and the organism. Experimental animals, mostly rats and mice, have been used in a great variety of basic studies, most of which are too esoteric for discussion here. The general aim of this work, however, is to learn the nature of radiation injury; how to prevent it, and how to treat it, ultimately in the human.

Early difficulties and disappointments with animal studies at Operation GREENHOUSE and BUSTER/JANGLE led to the development of laboratory radiation sources for greater economy, efficiency, and control of experimental variables. These sources include many emitters of nuclear radiation as well as two particularly satisfactory thermal sources—the Mitchell carbon arc, whose energy is usually emitted in the form of a standardized simulation of a nuclear weapon's thermal pulse; and the 30-inch searchlight, whose energy, about three times that of the Mitchell, is normally controlled by a precise square-wave shutter on which staff members hold a patent.

Studies of rat skin burns developed into investigation of more profound systemic effects such as erythrocytic fragility and led to the first Thermal Burn Conference, held at NRDL in 1953. They also were expanded to include burns from beta particles from P^{32} , a Sr-Y plaque (with a longer half-life than P^{32}) which produces about 25 rads/sec, and electrons from the Van de Graaff accelerated over a wide energy range—from the machine's upper limit of 2 MeV down to levels at which the electrons will penetrate skin only to a depth of 100 microns. Volunteers have exposed themselves to first degree thermal burns and, with the required approval of the Secretary of the Navy, to low-level beta radiation, attempting to add to the small store of data on the human. At present, long-term inter-species comparisons using large mammals are under way, particularly with neutrons, again in an attempt to extrapolate, eventually, to the human. *In vitro* studies of the inhibition of synthesis of DNA (a basic cell material) by sodium ions, which as [sic] among the products of ionizing radiation, are of interest to the cancer researcher. Studies of avoidance conditioning, wherein animals will quickly learn to avoid a place where they were given low doses of x- or gamma radiation, raise interesting questions about their sensing the presence of radiation. Other work has shown that the liver, thought to be insensitive to radiation damage, shows a high percentage of mitotic anomalies when cell division is accelerated. Successful inter-species transplants of skin and bone marrow are provocative to those studying radiation therapy. (OPNAV 5750-5 [1959])

(a) This was not totally foreign to the Navy's mission. A tightly closed vessel, especially a submarine, with multitudinous instruments involving luminous paint, could accumulate sizeable concentrations of radon. Hence, this foray had significance beyond the problems of uranium mining that were the traditional arena for concerns about radon.

In a report for fiscal year 1969 (USNRDL 1968),^(a) the following biomedical research enterprises were listed. This was work sponsored by the Bureau of Medicine and Surgery and directed by Drs. E. Alpen and G. F. Leong:

1. Radiation effects on cellular regulation
2. Biochemical basis of radiation sensitivity
3. Ontogenesis of the immune response
4. Partial body radiation—biological effects of shielding
5. Radiation effects on gastrointestinal tract function
6. Therapeutics and modification of radiation injury in mammals by biological and chemical means
7. Hazards of airborne radioactive materials
8. Alteration in physiological functions following exposure to ionizing radiation
9. Biological effects of microwave radiations.

Under Defense Atomic Support Agency sponsorship we find:

1. Higher energy neutron radiation effects on mammalian systems
2. Transport of fission products by marine organisms
3. Beta dose from fallout particles
4. SNAP^(b) effects on the ocean environment
5. Dose rate influences on large domestic animals
6. Effects of fallout on simple selected ecosystems.

To provide an even more versatile external radiation source, particularly one for neutrons, the laboratory installed a cyclotron in the late 1960s. The cyclotron was of the azimuthally varying field (AVF) variety, designed to produce extraordinarily high fluxes of 14-MeV neutrons by bombarding appropriate targets with protons or deuterons. Its principal application was to have been to radiobiological research. An initial beam had been developed just as the laboratory was disestablished in November 1969.^(c)

Other studies listed in the many reports from NRDL include more acute radiobiology and much interest in the mechanisms of radiation repair in cells and tissues, as well as the longer-term effects of the moderately high doses, e.g., renal neoplasia, arteriosclerotic changes, biochemical and metabolic alterations, and the growth and reproduction of irradiated animals.

Obviously, the NRDL had become a major laboratory for research in radiobiology, with emphasis on problems of military origin. Of pertinence to aquatic radiobiology were studies on the radiocontamination of marine life. A closed circuit aquarium system was developed, and various species of marine seaweed were cultured therein. Modalities studied besides uptake of radionuclides included possible effects on the sexual cycle of organisms with multiple developmental stages. Ion transport in plants was also studied in order to provide a greater understanding of hazards due to possible broadcast dispersion of radionuclides.

As the space program grew, the laboratory investigated possible inhalation hazards from toxic or radioactive materials potentially released in a space

(a) I am much indebted to Dr. Eugene P. Cooper, Naval Ocean Systems Center, San Diego, California, and a former director of NRDL, for an interview and permission to review in his office many unclassified documents that had been transferred from NRDL.

(b) See chapters 9 and 14.

(c) Details supplied by Eugene Cooper (1983).

vehicle abort or destruct; possible beta dose to tissue from radioactive particle debris was likewise investigated.

Unfortunately, any attempt to delve more deeply into the results of NRDL work than can be learned from the several OPNAV reports is frustrating indeed. Some of the work was published in conventional scientific literature and has been cited in earlier chapters. Large portions remained in NRDL reports. For reasons that will become apparent presently, it appears that there is now no single central source file of NRDL technical reports; at least no one seems to know of such a source. Therefore, this author has had to resort to tapping files of individuals who were at NRDL at one time or another and have kept from a few to many reports. These include, in addition to those already named, Drs. Victor Bond and Stanton Cohn at Brookhaven National Laboratory (BNL) and Dr. Charles Sondhaus at the University of California, Irvine. A partial listing of NRDL reports appeared in the 1959 Congressional hearings on fallout cited in chapter 12. This list, plus a truncated catalog of reports particularly pertinent to the subjects of this book gathered from several sources, is given as note 1 at the end of this chapter.^(a) Many reports that do not concern radionuclides have been passed by for this listing, as have reports and publications that do not involve research. Note 1 constitutes but a minuscule sample of work done over many years by a large and productive staff, but it provides the flavor of their activities bearing on research arising from fallout problems.

Why is it so difficult to obtain NRDL technical reports and to review their contributions in depth?^(b) In the summer of 1968, high Navy and Department of Defense (DoD) echelons decided that NRDL had accomplished its mission and should either go on to something different or shut down. Naturally, the first alternative was chosen, and the laboratory expected to be reoriented as the Navy Nuclear Center. This did not happen. That mission went instead to the Naval Ordnance Laboratory. On April 29, 1969, the NRDL was officially informed that it would be closed as of the end of 1969. The effect was, of course, catastrophic. Even though many of the lower-level personnel received assignments in other Navy laboratories, nearly all of the Division and Section Chiefs sooner or later went elsewhere (Cooper 1969).

Probably the worst feature of the operation was the random dissemination, if not outright destruction, of valuable equipment, including the almost new cyclotron, the laboriously assembled animal colony, and the loss of research records, even for work in progress. True, the records were originally slated to go to other cognizant Navy or other service laboratories. However, when the day of housecleaning arrived, most were arbitrarily consigned to Dempster dumpsters.^(c) Only a few reached other destinations in usable form. This was not one of the U.S. Navy's better performances!

Thus ended abruptly a laboratory that had developed a fine reputation and been graced by scientific and technical directors such as Paul C. Tompkins, Albert Behnke, Eugene Cooper, and Edward Alpen. An unanswered and perhaps unanswerable question is why the Navy, or any military laboratory, required such a widely diversified program in radiobiology when the Atomic

(a) Remember also the citations in chapters 3 and 9.

(b) Much of this discussion rests upon the interview held with Dr. Eugene P. Cooper already mentioned (Cooper 1983), and a draft document he prepared in 1969 (Cooper 1969).

(c) From discussion with Dr. Edward Alpen, March 1984.

Energy Commission (AEC) was at the time supporting handsomely the broadest possible program. Despite the ugly features of implementation of the closing, it may well be that the laboratory had indeed completed its mission. In any event, these occurrences explain why it is hard to find out what was really done except through published papers or by asking former personnel. The information of most pertinence to this book has been discussed or will be in connection with specific subjects.^(a)

B. The University of Tennessee-AEC Agricultural and Research Programs^(b)

This program also began around one of the weapons tests, viz., the Trinity shot at Alamogordo, New Mexico, in 1945. As described in chapter 12, grazing cattle received fallout on their backs, and many developed beta burns. Because of the loss in commercial value, the Army bought up several hundred of the cattle. Sixty of these arrived in Oak Ridge, where they were held for observation of possible long-term effects. When the AEC came into being, a contract was let in 1948 with the Agricultural Research Laboratory of the University of Tennessee. An old school building not far from the main road into Oak Ridge was renovated into a laboratory, surrounding open spaces were fenced off, and there began what was known for many years as the University of Tennessee-Atomic Energy Commission (UT-AEC) Experimental Farm. Financing came part of the time through the Oak Ridge Institute of Nuclear Studies, but the operation remained identified with the University of Tennessee through most of its existence. The dollars came from the AEC.

Cyril L. Comar, a plant physiologist and biochemist, who had already established a reputation for work using radioactive tracers in agricultural research, especially in mineral metabolism (see, for example, Comar 1953a,b), was persuaded to come as director. He proceeded to establish a broad research program whose origins lay in the problems of fallout. He was joined by F. W. Lengemann and R. H. Wasserman and later by John Thompson, Jr., all of whom were also interested in mineral metabolism. These men remained members of the Comar team for over two decades. Several veterinarians worked also at the laboratory. At least two of these established moderately long-term associations with the group, viz., John H. Rust and Bernard F. Trum. Rust went to the University of Chicago in 1959, while Trum went, in the same year, to Massachusetts Institute of Technology (MIT) and Harvard to manage a primate center. Other veterinarians took over to continue the experiments.

(a) The Armed Forces did not abandon radiobiology and nuclear medicine completely at this time. While the above events were occurring at NRDL, the Armed Forces Radiobiology Research Institute (AFRRI) had been established (1961) on the campus of the National Naval Medical Center in Bethesda, Maryland. As described elsewhere, the mission of this laboratory barely began to cover the areas of strength of NRDL. It was concerned at the outset primarily with the effects, particularly on performance, of very high doses of external radiation. It dealt hardly at all with radionuclide problems, and its work cannot, therefore, be considered in any detail herein. It was (and is) well equipped with irradiators, a research reactor, and it has sponsored good programs in basic molecular biology. It is still quite active and has a broad program.

(b) I am indebted to Dr. T. R. Noonan for providing early progress reports, a complete list of publications, and many reprints of work at this laboratory.

Let us look first at what became of the Alamogordo animals. Of the sixty Hereford cattle (forty-one cows, eighteen steers, and one bull),^(a) all but eleven had to be destroyed in 1951 because of anaplasmosis, a malady quite unrelated to radiation exposure. Despite this regrettable loss of statistical strength, the story continues until 1964 when the last cow died. By this time, Comar had gone to Cornell University (see next section), but a competent veterinarian (D. G. Brown) and colleagues carried on. They described the long-term effects of the fallout on these animals in 1966, over twenty years after the contamination event (Brown, Reynolds, and Johnson 1966).^(b)

There were ninety-four calves brought to weaning from these eleven cows beginning in 1948 (out of 114 possible "breeding years"). In addition, two calves were born dead and four that appeared normal at birth died before weaning. Evidently, this performance is not unusual in such herds.

Hemograms and other clinical tests were essentially negative. The most significant damage from irradiation was associated with the areas of the beta burns, i.e., "hyperkeratosis in the form of plaques and cutaneous horns on the skin of the dorsum" (Brown, Reynolds, and Johnson 1966). Three of the cows that survived fifteen or more years after receiving fallout on the skin developed squamous cell carcinoma at the site of the irradiation lesions. The radiation doses were estimated at 150 R of penetrating and 37,000 rad of beta radiation to the skin surface.

The lesions did not seem to affect breeding efficiency or relative fertility. Indeed, over the period before the anaplasmosis epidemic, the entire herd's performance was slightly ahead of the controls. This is illustrated in table 13.1, taken from an M.S. thesis by J. M. Bird at the University of Tennessee quoted by Brown, Reynolds, and Johnson (1966).

TABLE 13.1. Breeding Efficiency and Relative Fertility of Cows Exposed to Radioactive Fallout in 1945 During the Period 1948-1951*

Data	Irradiated cows	Control cows
No. of cow breeding years**	80	201
No. of conceptions	69(86%)	148(74%)
No. of abortions	2	4
No. of stillbirths	1	8

* Bird, J. M.: The Effect of Irradiation from Atomic Bomb Fallout upon a Group of Hereford Cattle. M.S. Thesis. University of Tennessee. Knoxville, 1952.

** Maximal pregnancies possible for the designated breeding period.

Source: Reset from Brown, Reynolds, and Johnson 1966. Reprinted with permission of the *American Journal Veterinary Research*, Schaumburg, Illinois, copyright 1966.

A picture of the last surviving cow from the Alamogordo herd is shown as figure 13.1.

- (a) There were also seventy-four controls of local origin raised with the Alamogordo herd.
 (b) This work is obviously not experimental, but it needs to be described as part of the laboratory's heritage.



FIGURE 13.1. Alamogordo Cow Number 52, the last surviving member of the herd accidentally exposed to fallout from the Trinity shot in July 1945, and calf. She produced sixteen consecutive calves, all apparently normal. Note the areas of lighter color on the back, site of the beta burns. In some animals, these areas became squamous cell carcinomas, but not in the majority despite a high beta radiation dose. Photograph taken in 1964. (Courtesy of Thomas R. Noonan, Comparative Animal Research Laboratory, Oak Ridge, Tennessee.)

The more strictly research enterprises at UT-AEC Farm concerned radioisotope metabolism. Even before the official facilities were ready, arrangements were made for Dr. Comar and his early colleagues, S. L. Hood and S. L. Hansard, to conduct preliminary studies on calcium metabolism using ^{45}Ca at the Special Training Division of the Oak Ridge Institute for Nuclear Studies. By 1949, nine projects were in the planning stages and two or three were started:

1. Bomb radiation effects on farm animals
2. Fission product metabolism in animals
3. Absorption and distribution of radiocalcium
4. Interrelationships of radiocalcium metabolism with other minerals, vitamins, and hormones
5. Radiation effects on reproductive function in farm animals
6. Radioisotopes in poultry nutrition
7. Radioisotopes in the physiology of milk secretion
8. Behavior and fate of radiocalcium after incorporation in soil
9. Relation of soil types to availability of nutrients.

By 1951, all of these studies had been activated, and a tenth project, "External Radiation Studies in Large Animals," had been added. For the latter, a large animal exposure field was developed using a multicurie radioisotope source of gamma radiation.

By far the best known of the pure research enterprises concerned the metabolism of pairs of elements, e.g., strontium/calcium (see chapter 12 for discussion of the Sunshine Unit based on this ratio) and the presence and reasons for discrimination between such pairs of elements. Since this work involved fundamental concepts that apply to all of the metabolic research stimulated by the fallout problems in the several laboratories, we will discuss it as an entity in section III.

There was also much work on the behavior of strontium, cesium, and other radionuclides in fallout in a variety of farm animals. Important results came out of the studies to determine the effects of various factors both in the environment and within the animals, including transplacental transfer of important radionuclides not in fallout (Hansard 1969). The program confirmed in large measure the basic phenomena seen in small laboratory animals, as described in chapter 8. Some fairly heroic techniques were developed, e.g., to separate urine from feces in the cow, as shown in figure 13.2.



FIGURE 13.2. Arrangement for separate collection of urine and feces from the dairy cow; the large animal version of a metabolism cage, used at UT-AEC Farm. The laboratory also designed a metabolism unit for radioisotope balance studies with dogs (see Hansard 1953). (Courtesy of John Thompson, Jr., now at Cornell University, from his collection of Oak Ridge pictures.)

The basic research on mineral metabolism involved much work with bone. The laboratory developed a strong capability with autoradiography with particular help from William E. Lotz, who was Cyril Comar's first Ph.D. student at the University of Tennessee (1950), and from George A. Boyd and John C. Gallimore, who came to Oak Ridge from the University of Rochester (Comar, Lotz and Boyd 1952; Lotz, Gallimore, and Boyd, 1952; Lotz and Johnston, 1953).^(a) The work utilized such well-established tracers for mineral metabolism as ^{45}Ca and ^{32}P , in addition to the radionuclides in fallout. Both animal and plant materials were utilized.

The work at Oak Ridge continued for many more years after the departure of Comar and some of his colleagues (see next section). Key staff members were D. G. Brown, M. C. Bell, J. K. Miller, F. R. Mraz, R. A. Reynolds, G. E. Spalding, and others. S. L. Hansard, who had been with the laboratory from the beginning, assumed many of the administrative duties of scientific direction and continued his scientific work. In due course, the laboratory became the Comparative Animal Research Laboratory (CARL) of the University of Tennessee and Department of Energy (DOE). Among other personnel changes, Dr. Thomas Noonan, who spent many years at the Rochester Project, took over as research director. The laboratory placed less emphasis on the radioisotopes in fallout (obviously the problems had become less urgent) but kept on with more generalized tracers and a few continuing enterprises such as iodine metabolism. Also, facilities were installed to work with the transuranic elements whose importance had grown over the years. There was more research emphasis, relatively, on external radiation effects. The laboratory participated very actively in efforts of the university, the state, and the U.S. Office of Civil Defense and its successor agency, the Defense Civil Preparedness Agency, to inform the agricultural community of the possible effects of fallout on farm animals and crops and possible measures to take in the event of contamination.

Not coming under headings to be discussed in sections III and IV is work combining exposure to radionuclides and external gamma radiation (e.g., Bell, Lowrey, and Winthrow 1967), the toxicity of very high levels of certain radionuclides on avian embryos (Mraz, Wright, and Ferguson 1964; Wright and Mraz 1965; Mraz 1966, 1969), embryonic uptake of calcium and strontium (Mraz 1970), and the effect of dietary strontium on reproductive performance in poultry (Mraz, Wright, and Ferguson 1967).

Dr. Noonan retired in due course, and CARL became something of a holding operation. Indeed, it seemed to be headed toward termination. Instead the laboratory was consolidated into the Medical Division of the Oak Ridge Institute of Nuclear Studies (ORINS)—Oak Ridge Associated Universities (ORAU) under the temporary direction of Dr. Clarence Lushbaugh. Dr. William Burr, formerly director of the Division of Biomedical and Environmental Research at the DOE Headquarters, has agreed to direct the former CARL program. While the original mission may be considered completed, the important metabolic work will probably be combined with other work of ORAU and continued under Dr. Burr's capable direction.

(a) Lotz collaborated with Comar and others at the UT-AEC Farm on several other projects. He also worked in the Medical Division of the Oak Ridge Institute of Nuclear Studies before going to Washington to the AEC's Division of Biology and Medicine (see chapter 9).

Research at the UT-AEC Farm provided some very basic concepts as well as confirmation in large animals, in plants, and in other agricultural materials of the findings described for laboratory animals in chapter 8. Laboratory research and practical agricultural enterprises had to compete for manpower and funds. There were over 650 publications up to 1977. A list of selected publications pertinent to this chapter, in addition to those cited specifically in the text, along with a few others is given as note 2 at the end of this chapter.

C. Cornell University^(a)

It must have been 1956 or earlier that plans were made to organize a radiobiology program at the New York State College of Veterinary Medicine operated by Cornell University. It was cast very much in the mold of Cyril Comar's program at Oak Ridge, and in 1957 Comar transferred his activities from Oak Ridge to Ithaca. Wasserman went to Cornell shortly thereafter. Lengemann came on a visiting basis in the summer of 1958 and permanently in 1959. John Thompson, Jr., also transferred from Oak Ridge. There were facilities on the campus, and a separate farm facility was built away from the campus, which incorporated a multicurie gamma source for irradiation of animals of all descriptions. The operation was designated the Laboratory of Radiation Biology and was supported by the AEC, the Department of Agriculture (USDA), the Defense Atomic Support Agency, and the U.S. Public Health Service (PHS). It began as part of the Department of Physiology of the Veterinary School. Before long, it grew into departmental status in its own right and was designated the Department of Physical Biology.

We do not have any written record of the *raison d'être* for developing another laboratory with a mission so similar to the UT-AEC farm or the willingness of the AEC to underwrite two such similar enterprises. We can make some guesses however. The Cornell enterprise began near the height of the fallout controversy. Perhaps the AEC desired an agriculturally oriented laboratory more distant from one of its prime installations. Perhaps, particularly since the work involved much need for collaboration with physiologists, pathologists, nutritionists, biochemists, and so forth, the potential for in-situ liaison on a university campus weighed heavily. (The University of Tennessee campus was about thirty miles from the Oak Ridge farm.) The chances for developing a strong academic department were better at Cornell. The development of educational programs would be simpler at Cornell. Indeed, it turned out that the Cornell Department of Physical Biology became a center for graduate education and for summer and academic year institutes in radiobiology. Alison P. Casarett, who migrated to Cornell from Rochester and who wrote a well-known textbook, *Radiation Biology* (Casarett 1968), was largely responsible for the success of these many training and education functions.

The scientific program was naturally very similar to what had been done at the UT-AEC Farm at Oak Ridge, minus, of course, the Alamogordo cattle. A listing follows of the experimental studies under way in a typical year (1964-1965) when the fallout work was a prime stimulus. It is taken from the Annual

(a) I am indebted to Drs. A. P. Casarett, F. Lengemann, and J. Thompson, Jr., for information on the development of the Laboratory and its programs. Unfortunately, the written record is very sparse.

Progress Report, Cornell University Department of Physical Biology, 1964-1965 (courtesy of Drs. F. Lengemann and A. P. Casarett, Cornell University).

A. Phase I—Fission Product Metabolism and Response in Laboratory and Domestic Animals

1. Retention of Strontium as a Function of Age in the Beagle
2. Incorporation of Strontium and Calcium into Human Chromosomes
3. The Transport of Calcium, Strontium and Barium Across Rabbit Duodenum *In Vitro*
4. Vitamin D Enhancement of the Unidirectional Fluxes of Calcium Across Rachitic Chick Ileum and Rat Duodenum
5. Predicting the Total Projected Intake by Man of Radioiodine from Milk
 - I. The Situation Where No Countermeasures are Taken
 - II. The Situation Where Countermeasures are Employed
6. Predicting the Total Intake of Radioiodine by Humans Consuming Goat's Milk
7. The Turnover of Cesium in Rats as Affected by Temperature, Water Consumption, Cellulose Content of Diet, and Hypothyroidism
8. Urine/Diet Studies
9. Genetic Studies on Cell Wall Mutants of *Staphylococcus aureus*
10. Erythrocyte Loss and Restitution in Ovine Haemonchosis

B. Phase II—Planning Study for Evaluation of Radioactive Contamination of the Food Chain

1. Fluid Milk Consumption: Variability and Relationship to Radionuclide Intake
2. Nutritional Aspects of Food Chain Contamination
3. Sr^{90} and Cs^{137} Studies in Selected Vegetable Crops
4. Radionuclide Prediction Studies
5. World Fallout Data Assessment and Summaries

Later, the program on the campus broadened to include aspects of neurobiology. Some of them were oriented toward radiation effects, especially measures of performance following high doses of external radiation and also possible subtle behavioral changes at lower doses, but there was much basic neurobiology. The connection to the original problems of radionuclide metabolism continued, nevertheless, with work on environmental transport, membrane transport of alkaline earths and the mechanisms involved, strontium metabolism and secretion in milk. These included a modicum of work on human subjects for tracer studies, secretion of strontium in human milk, etc.

Work pertaining to the many aspects, both laboratory and environmental, of atomic energy and agriculture carried out at Cornell is cited, in part, in the list of selected publications from Cornell shown as note 3 at the end of this chapter. There was a very useful annotated bibliography of strontium and calcium metabolism by Wasserman and Comar published by the USDA (Wasserman and Comar 1961).

In early 1975, Comar moved back to California, where he had been educated, as director of the Environmental Assessment Department of the Electric Power Research Institute in Palo Alto. There he gradually applied the talents and methodology developed originally around the problems of fallout to those of other forms of energy generation, particularly coal. At Cornell, Lengemann, Johnson, Wasserman, and others kept the radionuclide and mineral metabolism program going; Casarett and others continued to work with external radiation

and the education program until Casarett entered the administrative echelons as dean of graduate studies and later vice provost and provost. However, the department eventually lost its identity. After some intermediary stages, the work is now back in the Department of Physiology of the Veterinary College.

It is probably fair to say that the motivation for current research at Cornell is no longer the problems of fallout; yet they stuck very close to the basic program for many years and followed through at the mechanistic level to a very satisfying degree. We will review some of the specifics in later sections.

D. University of California at Davis, Radiobiology Laboratory and Later Laboratory of Energy Related Health Research^(a)

This project qualified as one of the postwar "King-Sized Experiments" and has had implications for the entire field of radionuclide metabolism. Thus, its origin and the development of its programs were described in chapter 8. (See "Davis Beagle Project.") The primary radionuclide was ^{90}Sr , with ^{226}Ra as a tie-in to both the Utah project and experience in humans. The primary route of administration was via the diet. The milieu was again a School of Veterinary Medicine, and there were strong ties to agricultural research. For these reasons, most of the results of the Davis enterprise can be regarded as related directly to the problems of fallout and should be described here, even though the development began shortly before fallout problems reached compelling proportions.

The personnel, the complete plan of the main experiment including the dosage levels, and a few details of the protocols are given in chapter 8. In section IV of this chapter, we will review, under "Strontium," the primary thrust of the results. It should be noted that the dosage regimen was rather different from many of the other experiments discussed thus far in this chapter. Besides utilizing the oral route, the intake was more or less continuous over long periods. It thus resembled the large experiment with iodine in sheep done at Hanford (chapter 8). A basic question was not only how intake via the diet might influence metabolism and effects, but how more or less continuous intake might modify these as compared to a single injection, as in the Utah experiment. As we will see, there were significant modifications of both metabolism and effects.

There were many ancillary experiments directed at mechanisms, species comparisons, isotopes other than strontium, such as iodine, effects in pregnant and fetal animals, etc. These too will appear largely in section IV. The last animals from the main experiment are approaching the end of their expected life spans. Emphasis on mechanistic aspects has been expanding. Also, the base of the work has gone far beyond radionuclides of fallout, even nuclear energy to other forms of energy generation (hence, the name change to "Laboratory of Energy Related Health Research").^(b) It remains to be seen whether or not completion of the original experimental protocol will lead to termination of this laboratory as an entity or if it can proceed on the new tracks it has laid, particularly now that the culmination of many hints regarding mechanisms gathered during the days of confining pragmatic operations are beginning to show signs of coming to fruition.

(a) I am indebted to Dr. Marvin Goldman for an overview of the work at this laboratory, an interview, and background literature.

(b) An extensive aerosol and inhalation toxicology laboratory has been developed as part of the Davis enterprise.

E. Southwestern Radiological Health Laboratory^(a)

In chapter 12, we saw the development of offsite surveillance activity, particularly for the Nevada Test Site (NTS), under the aegis of the PHS. A small group of PHS officers, led by Oliver Placak, spearheaded this activity. In 1954, with the signing of an official Memorandum of Understanding with AEC, a small staff of regular commissioned PHS officers was permanently stationed in Nevada to head up the program that had been operated largely by assigning Reserve Officers on temporary duty. In 1959, with the fallout controversy heating up still further, the PHS's new Division of Radiological Health established the first of the three regional radiological health facilities, this one in Las Vegas. They called it the Southwestern Radiological Health Laboratory (SWRHL).^(b)

While the nucleus was the radiological safety program, research projects gradually developed, some of which concerned methods for removal of radioisotopes, particularly strontium, from milk and other foods (chapter 12). Early there was much work on development of instrumentation and methods and field-type research around the indigenous animals on the test sites. In 1963, an experimental farm was begun on a thirty-acre plot on the NTS. Full facilities were completed there in 1966. There was a beef herd, mostly kept on the range, and a milking herd of dairy cows that was kept in corrals. The operation continued until 1979. Crops were planted and irrigated under such conditions that simulated fallout from controlled releases could impinge upon the soil and foliage. Major emphasis was placed upon the transport of radioiodine through the soil-forage-cow-milk chain. The agronomic aspects were described by Daley and Smith (1969).

Pictures of the laboratory buildings in Las Vegas, the farm at NTS from near and far, and the SWRHL version of a bovine metabolism cage are shown in figure 13.3A, B, C, and D.



FIGURE 13.3A. Southwestern Radiological Health Laboratory, Las Vegas, Nevada. (Courtesy of U.S. Department of Health, Education and Welfare 1966.)

(a) I am indebted to Mrs. Geneva Douglas, former director of this laboratory's Information Services for capsule histories, a complete list of publications, selected reprints of the published work, and for a review of the section. Also, Dr. Melvin Carter, the laboratory's second director, provided much information, an interview, and several pictures.

(b) The others were the Northeastern Radiological Health Laboratory in Winchester, Massachusetts, and the Southeastern Radiological Health Laboratory in Montgomery, Alabama. We have already mentioned work from these installations.

FIGURE 13.3B. (Right) Moderately close-up view of the Southwestern Radiological Health Laboratory on the Nevada Test Site. The dairy herd was kept in corrals in the foreground, the crops potentially exposed to fallout were grown on an irrigated field in the near distance. Not shown is the beef herd that was on more open range. (Courtesy of Geneva S. Douglas, U.S. Environmental Protection Agency, Las Vegas.)

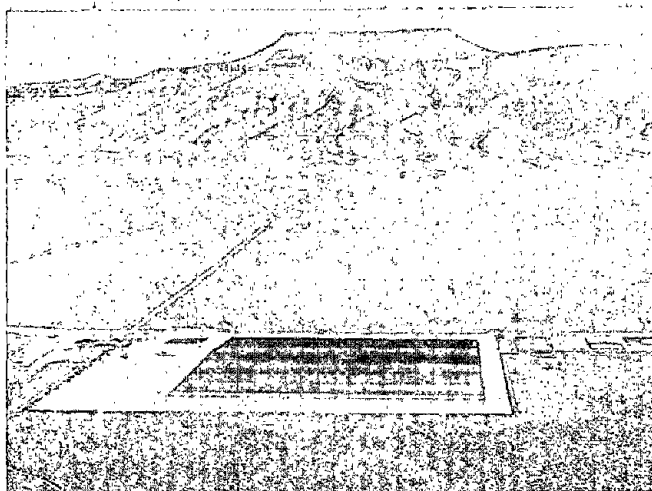
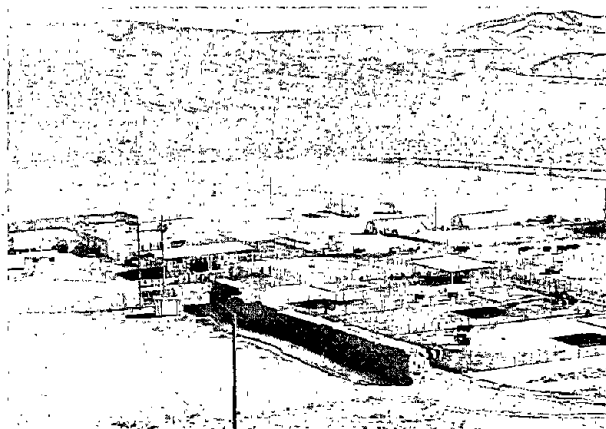


FIGURE 13.3C. (Left) Further out view of the Southwestern Radiological Health Laboratory Farm on the Nevada Test Site. The irrigated crops grown for forage are on the dark rectangle in the center. (Courtesy of Geneva S. Douglas, U.S. Environmental Protection Agency, Las Vegas.)

FIGURE 13.3D. (Right) The Public Health Service version of a bovine metabolism cage as installed at the large-animal farm at the Nevada Test Site. These animals were fed in part with forage grown in the area depicted in figure 13.3C. (Courtesy of Geneva S. Douglas, U.S. Environmental Protection Agency, Las Vegas.)



It was possible to introduce variations in the soil and other conditions, even to prepare and release on the crops aerosols tagged with ^{131}I and determine the passage of the isotope from such a source through the food chain (see, for example, Stanley, Black, and Barth 1969; Douglas, Black, and Barth 1971; James et al. 1970; Mason, Black, and Barth 1971; Black et al. 1971).

In another approach, hay bales were placed from thirty to fifty miles from ground zero of a nuclear burst, and the hay, after recovery, was fed to dairy cows at the farm as a controlled ingestion experiment (Black, McNelis, and Bretthauer 1972). In other cases, the cows were exposed directly to the effluent cloud (Black et al. 1971). The results of these and related experiments will be viewed in combination with other research in section IV.

A novel approach to determining the radionuclide composition of the diet ingested by the cattle was the preparation of rumen-fistulated steers. (a) The indwelling tube was capped with a lid like a jar. This indwelling hardware seemed to cause the animals no discomfort. One member of the beef herd, "Big Sam," seemed very proud of his special device and willingly showed it at special events, including county fairs. A picture of "Big Sam" is given as figure 13.4.



FIGURE 13.4. "Big Sam," one of several rumen-fistulated steers in the beef herd kept at the Southwestern Radiological Health Laboratory Area of the Nevada Test Site. The cap of the fistula is easily removed to provide samples of the range diet and, on analysis, its radionuclide content. It is assumed that the diet of the rumen-fistulated steers imitates that of the entire herd. Such animals have been on the range for many years. (From "Environmental Information," U.S. Environmental Protection Agency, June 1979, courtesy of Geneva Douglas.)

By 1966, SWRHL had grown to a staff of 220 and had five buildings on the campus of Nevada Southern University (now University of Nevada at Las Vegas; see figure 13.3A). These facilities were provided through the U.S. Congress and the state of Nevada and leased to the PHS. In addition to excellent laboratories for radiochemical work, the facility was well provided with whole-body counters for people and animals and much paraphernalia for environmental sampling. At NTS, the special facilities pictured in figure 13.3B, C, and D allowed work under field conditions at higher levels of radioactivity.

In 1970, as we know, the new U.S. Environmental Protection Agency (EPA) took over SWRHL from the PHS. There has been a gradual transfer of the

(a) A surgical opening made in the animal's side provided easy access to the rumen so that the contents of the forestomach could be sampled.

research and monitoring to nonradioactive substances. There was some collaboration with the Nevada Applied Ecology Group of DOE (see chapter 14) on problems of residual contamination of NTS with long-lived transuranics. The program has deemphasized research somewhat in recent years, but the monitoring and environmental assessment capabilities have remained strong.

In the formative years (1953–October 1967), SWRHL was directed by Oliver Placak, who was ubiquitous around the Nevada tests. During the period of most rapid research growth and the period of transfer to EPA, the director was Melvin W. Carter (March 1968–August 1972), who is now at the Georgia Institute of Technology in Atlanta. He was followed by Delbert S. Barth (September 1972–September 1976), some of whose work we have already cited. There was new experimental work on individual radionuclides given to cattle and a gradual shift of the monitoring programs to contemporary problems such as tritium, krypton, uranium in mill tailing, etc., but the iodine work continued more or less without serious interruption.

Other activities at SWRHL concerned some of the special events reserved for discussion in chapter 14. On balance, it can be said that SWRHL never lost its roots or commitment to environmental monitoring and research on environmental transfer phenomena and that it managed a fine blending of an occasional pure research venture in a milieu of assessment and monitoring.

F. Other U.S. Public Health Service Laboratories

In chapter 10, we reviewed work done at the PHS laboratory in Montgomery, Alabama, on radiokrypton and by a PHS officer (Cahill) working at Rochester and later at the EPA's Research Triangle installation in North Carolina on tritium. These researchers were stimulated in part by the problems of fallout, in part by general problems of environmental contamination with radionuclides.

A fairly vigorous program was developed on radionuclide metabolism and effects at the Robert A. Taft Center in Cincinnati. This was called the Radionuclide Toxicology Laboratory and was headed by a PHS officer, Jerry F. Stara. It emphasized strontium in cats, and a fairly extensive outdoor breeding colony for cats was developed. However, there was work also on iodine and the usefulness of various pharmaceuticals for repressing uptake of radionuclides from the gut (chapter 19).

In 1968, the PHS decided to move the Radionuclide Toxicology Laboratory from Cincinnati to the Twinbrook Laboratory in Rockville, Maryland. This may have been partly because the Cincinnati laboratory was primarily concerned with engineering, particularly industrial hygiene engineering. The work continued for many years but at diminished intensity. Publications, particularly on long-term pathological effects in the cat, appeared as late as 1972. We will review the results of PHS research with strontium and iodine in section IV.

There was some experimental work from the Robert A. Taft Center on experimental uptake of ^{85}Sr by freshwater organisms (Brüings 1965). This was a factorial study of the effects of varying the concentrations of calcium, magnesium, sodium, and potassium on the uptake of ^{85}Sr by small bluegills in laboratory aquaria. Of the four cations used, only calcium had a significant effect. There was also a study in a small pond to determine total uptake of the strontium in a natural environment. The amounts in the organisms never exceeded 0.5% of the amount added, and this was related to the age of the fish. Only about a quarter

of the added "soluble" ^{85}Sr remained in the dissolved phase over an eighty-day experimental period.

We are already aware of the important part played by physicians from the PHS in the investigation of possible thyroid pathology in the Utah and Nevada residents exposed to fallout from NTS (chapter 12). Much of this was coordinated by the Radiation Bioeffects Program in Rockville. Arthur H. Wolff was chief of the program until the midsixties. He was replaced by William A. Mills when Wolff was asked to spearhead a new activity concerning consumer products. Norman Telles headed the radiation oncology and pathology effort, which involved both laboratory and epidemiologic approaches.^(a)

Overviews of the PHS program, variably called "Radiological Health Research" or "Radiation Bioeffects," can be seen in annual summary reports (PHS 1965-1966, 1967, 1968, 1970).^(b)

II. Special Programs at Established Laboratories

While the contrast between the efforts depicted in section I and those to be discussed in this section is largely a matter of context and *raison d'être*, and the actual results can be discussed more or less in unison, it is convenient to describe separately those programs that were added to ongoing work in well-established laboratories to attack some phase of the fallout problem. Included are only those entities that could be regarded nominally as "special programs," i.e., that probably would not have been undertaken without the stimulus of the problems of weapons-testing fallout. They, of course, tie closely to research activities in the same laboratories reviewed in earlier chapters or to be considered in chapters 19 and 20. General descriptions of the work appear in this section.

A. Argonne National Laboratory

The chief addition to the Argonne National Laboratory (ANL) program that we might attribute to fallout problems was increased emphasis on the effects of chronic administration, particularly of strontium isotopes. The experiments with mice for determining toxicity ratios and their results were taken up in detail in chapter 8. There was further work with mice and studies with beagles. Both were carried out by Miriam Finkel and her colleagues. Probably one of the most

(a) Work with radionuclides at the PHS laboratories that was not stimulated by or related to problems of fallout concerned naturally occurring heavy elements, such as polonium, radiolead, and some of the other components of the radon, radon-daughter series, and also Thorotrast. This work was headed by R. L. Blanchard with collaboration from S. C. Black among others. There were, of course, many PHS research programs concerned with external radiation sources. The most extensive was the Collaborative Radiological Health Laboratory located on the campus of Colorado State University at Fort Collins, which involved use of a barrier-maintained colony of beagles. To the extent that it focused on long-term effects of radiation, it could be said to have a bearing on the problems of fallout. The National Institutes of Health also had a program concerned largely with external radiation sources and basic radiobiology.

(b) I am indebted to Dr. John Villforth, long-time director of the PHS and later Food and Drug Administration activities in the field of radiological health, for supplying copies of these reports and other publications.

germane summaries for our present purpose is the one at the Symposium on Radioisotopes in the Biosphere held in Minneapolis (Finkel, Biskis, and Bergstrand 1960). The work with dogs was summarized by Finkel and colleagues at the Davis symposium on strontium (Finkel et al. 1972).

Finkel has long held the idea that initially high dose rates of low linear-energy-transfer (LET) radiations such as those from ^{90}Sr - ^{90}Y were more effective than constant low dose rates in producing tumors for the same total absorbed dose. Thus, she expected greater effectiveness of single intakes with their high initial radiation dose rate compared to a more constant intake with lower dose rates even at comparable total doses. Experiments were carried out with mice to test this hypothesis. Other experiments involved injecting beagles five times a week for one year for comparison with a single injection and thus for comparison with the results of the Utah beagle experiment. This was not a large program compared to the major beagle programs, but it served as a link between the extensive work at ANL with mice and the large dog experiments elsewhere. There was also an experiment in which mice were maintained on diets containing a constant ^{90}Sr -to-stable-calcium ratio throughout life. Each of these will be reviewed, as required beyond what was discussed in chapter 8, in section IV of this chapter.

During the active phases of fallout work, Finkel appraised the situation in a review prepared for *Science* (Finkel 1958). The potential danger to humans was evaluated on the basis of the animal experiments. She extrapolated the dose-response curves from these experiments and the results to date of the comparative toxicity work then in progress. She concluded that ^{90}Sr may be seven to fourteen times as toxic in humans as in mice. Nevertheless, the data led her to conclude that there was a very small probability that there was or could be a linear no-threshold dose-response relationship to ^{90}Sr in humans. She proposed a minimum effective dose for ^{90}Sr in humans of 6 to 15 μCi . Comparison of this to the calculated body burdens from fallout (on the order of 0.0002 μCi and a predicted steady-state value of about 0.02 μCi) led Finkel to conclude that "the present contamination with ^{90}Sr from fallout is so much lower than any of these levels that it is extremely unlikely to induce even one bone tumor or one case of leukemia" (Finkel 1958, p. 641).

This conclusion drew fire from many of the participants in the fallout polemic then in progress and came into discussions at the 1959 Congressional hearings (see U.S. Congress 1959 in chapter 12). Linus Pauling and colleague Barclay Kamb at Cal Tech prepared a detailed statistical analysis of the data Finkel used (Kamb and Pauling 1959). It was published in the *Proceedings of the National Academy of Sciences* and reproduced in the record of the Congressional hearings.

Briefly, Kamb and Pauling concluded that there were far too few animals in the experiment to allow any conclusions regarding linearity or nonlinearity of the dose-response curves. Indeed, they calculated that to establish statistical validity for one choice over another at 90% confidence would require over a billion mice in each dosage group.^(a)

(a) This author can see how such a large number would be needed to validate the points at levels such as 0.0002 μCi but is puzzled that the required group size would not decrease as the dose increased. Some of the doses in Finkel's experiment were rather high.

The argument is directed as much at the life-span shortening data as at the production of osteogenic sarcomas. It cites the fact that other functions, e.g., the Gompertz function, which is essentially linear, could fit the data quite well, and they devised some equations of their own. They presented several figures in which equations they derived fit Finkel's experimental points satisfactorily. They conclude that the only prudent course is to assume linearity and characterize Finkel's conclusion, quoted above, as "not justified." (a)

Dr. Finkel's conclusions were announced in the press. So were Dr. Pauling's criticisms. It is stated that Finkel wrote a reply to Pauling's "letter to the editor" of the *New York Times* (November 16, 1958) on November 30, 1958. Unfortunately, I have not been able to view a copy of this reply but can assure the reader that it was not a capitulation. There never can be a direct experiment that can establish dose-effect relationships in these very low dose realms. Therefore, opinions can legitimately differ. (b)

B. University of California at Berkeley

As the seat of the original biomedical work on fission products (chapter 6), Berkeley hardly needed to mount a special program to make significant contributions to research bearing on fallout. Yet a few items need description here.

First it should be pointed out that the very first paper on the secretion of radiostrontium in cow's milk came from prewar work at Berkeley. Erf and Pechier (1940) used ^{89}Sr as a surrogate for ^{45}Ca because they had difficulty obtaining the latter in sufficient yield from the cyclotron and because of the difficulty in measuring the very soft beta particle of ^{45}Ca . They injected two cows intravenously and measured the secretion of ^{89}Sr in milk for 102 hr. It was about 7.9% and 11% of the dose, respectively.

An experiment with ^{90}Sr in the rhesus monkey was begun quite early by Pat Durbin (chapter 8) with encouragement from Joe Hamilton. The experiment contained forty adolescent and adult female and male rhesus monkeys aged two to twelve years at the start of the experiment. They received from 0.5 to 20 μCi $^{90}\text{Sr}/\text{kg}$ (3.5 to 168 μCi per animal) and, except for two short-term animals that received 50 $\mu\text{Ci}/\text{kg}$, were followed for up to twenty years after the single injection (intravenous, intraperitoneal, or intramuscular). Despite what appear to be moderately high levels of injected radionuclides, no biological effects were detected. Thus, the experiment became largely a metabolism study. It provided important data on retention of ^{90}Sr in a primate over a twenty-year span of observations. These will be discussed under strontium in part IV of this chapter. A summary of the experiment was provided by Durbin and colleagues at the Third International Congress of the International Radiation Protection Association held in 1973 (Durbin et al. 1974). They concluded that rhesus

(a) Does this sound familiar? It should. The polemic is still going on even though the radiation protection fraternity has largely adopted the linear hypothesis or varieties thereof (chapter 16) as prudent for planning purposes.

(b) It could be argued that this discussion belongs in chapter 12, along with the general discussions that took place at the Congressional hearings. It is placed here because the conclusions were drawn directly from specific research data, not a generalized statement such as "the amounts found were well below established maximum permissible exposures." Also, the response from Pauling bore specifically on these research data and was a sophisticated research contribution in its own right.

monkeys of varying ages provide a suitable model to evaluate the long-term metabolism of the alkaline earth elements in larger species, including humans.

There was also work at Berkeley, but not in the Radiation Laboratory, on the uptake of fission products by plants.

C. Brookhaven National Laboratory

The key role played by BNL in the care and study of the Marshall Island inhabitants was described in chapter 12. Stanton H. Cohn set up the whole-body counting facility at Brookhaven soon after he transferred from NRDL and has used it for many years both for measurement of radionuclides from fallout in the general population and in the Marshallese and for experimental work involving both humans and animals. His years at NRDL could not help but sustain his interest in fallout problems, while his general interest in mineral metabolism has led to much basic work on bone.^(a)

Typical experiments of the 1960s, when the fallout problems were of overwhelming importance, are:

1. effect of aging and x-irradiation on the kinetics of skeletal metabolism in the rat (Cohn 1961);
2. diet-induced changes in the exchange and accretion of radiostrontium by rat skeleton (Cohn, Nobel, and Sobel 1961);
3. turnover of ^{85}Sr in man as determined by whole-body counting (Cohn et al. 1962b);
4. influence of dietary stable strontium and calcium on the turnover of bone-fixed ^{85}Sr in man (Cohn et al. 1962a);
5. comparative kinetics of ^{47}Ca and ^{85}Sr in man (Cohn et al. 1963a);
6. study of the uptake and transfer of fallout ^{131}I in pregnant women (Cohn and Gusmano 1963);
7. long-term ^{137}Cs turnover in man as measured by a whole-body counter (Cohn et al. 1963b);
8. cesium-137 metabolism in man (Rosoff, Cohn, and Spencer 1963);
9. effect of magnesium on the uptake and retention of radioactive strontium (Clark et al. 1964);
10. metabolism of ^{65}Zn in man (Spencer et al. 1965);
11. decrement in radiostrontium retention following stable strontium prefeeding in the growing rat (Teree, Gusmano, and Cohn 1965);
12. strontium and calcium skeletal discrimination determined by compartmental analysis (Cohn et al. 1966);
13. kinetics of strontium and calcium metabolism in the rat (Cohn and Gusmano 1967);
14. evaluation of the parameters of strontium metabolism in the rat as a function of age (Gusmano et al. 1968).

Gradually, the research turned to neutron activation analysis, studies of osteoporosis and other bone diseases, and studies of calcium metabolism.^(b)

(a) In chapter 9 we described Cohn's work in the inhalation field, including a study with ^{85}Kr at BNL.

(b) The H. Spencer in the citations above is Dr. Herta Spencer, first at Montefiore Hospital in New York and later at Hines Veterans Hospital in Illinois. Dr. Spencer ran an important metabolism ward for studies on man and collaborated extensively with Dr. Cohn. We discuss her work in some detail in chapter 19.

Some of the work cited above will be woven into our discussions of strontium and cesium in section IV. There can be no doubt that experience with the fallout problems determined the course of much basic research at Brookhaven and directed the career of Stanton Cohn as the Marshallese problems had directed Conard and others (chapter 12). Indeed, Cohn stated in a personal interview, "My specialty is calcium because of fission products and especially strontium" (Cohn 1982).

The resemblance between these activities and those of Comar's group (UT-AEC Farm and Cornell University) is obvious. The emphasis in the BNL studies was, of course, much more on man.

D. Battelle, Pacific Northwest Laboratories (Hanford)

We saw some of the measurement activities that were carried out at Hanford in Richland, Washington, and around the test sites by Hanford personnel in chapter 12. Since Hanford was the original installation deeply involved with problems of environmental contamination (chapter 11), it is not easy to earmark specific research there as being "stimulated" by the fallout problems. There were no projects overtly designated as having been so stimulated. Nevertheless, pertinence to fallout problems is obvious for some of them, and many have pertinence whether or not conceived for the purpose. Thus, the large experiment with iodine in sheep, which obviously was begun well before fallout had become a cause célèbre, had its origin in the finding of local contamination as discussed in chapter 8; it will not be repeated here. On the other hand, a large experiment with strontium in miniature swine, begun slightly later, was only touched upon in chapter 8 and was clearly related to fallout problems. Also, work at Hanford on strontium in rats was not discussed at all in chapter 8. This, plus work on the behavior of pairs of elements, nutritional considerations in the metabolism of strontium, work on cesium, and a large amount of field and laboratory work with plants, have all been reserved for present considerations.^(a)

We present below a capsule summary of the nature of the enterprises at Pacific Northwest Laboratory (PNL) and a few details so that the contributions of the Hanford group can be seen uncluttered by the details of the results of other work.

1. The Experiment with Strontium-90 in Swine

The development of the miniature swine used in this experiment is described briefly in chapter 8. The enterprise was a feeding experiment involving over eight hundred swine. The levels, fed individually with the morning ration of feed, were 1, 5, 25, 125, 625, and 3,100 μCi per day. These dosage levels were chosen to fit approximately the expected body burdens in the Argonne and Utah dogs that were receiving strontium intravenously and the large feeding experiment at the University of California at Davis. It extended over three generations. The first generation entered the experiment at nine months of age. The second and third generations were exposed throughout life, beginning in

(a) The enormous efforts at PNL on inhaled radioisotopes are described in chapters 9 and 10. These involve many of the fission products as well as transuranic elements. It was considered advisable to review all of the inhalation toxicology (pulmonary radiotoxicology) together in those two chapters; it will not be repeated here. The work includes strontium, ruthenium, and iodine in particular.

utero. Thus, there were many resemblances in protocol between this experiment and the one with iodine in sheep described in chapter 8.

The general protocol is outlined in figure 13.5, taken from a moderately early report by McClellan et al. (1962). In addition to the swine listed in the figure, there were 270 untreated animals that served as controls. Results are discussed in section IV of this chapter.

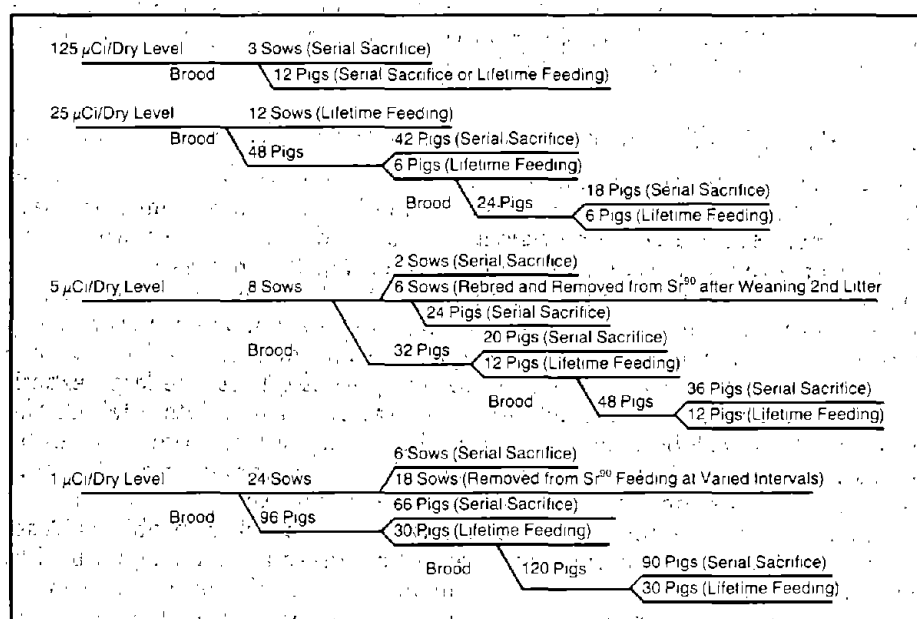
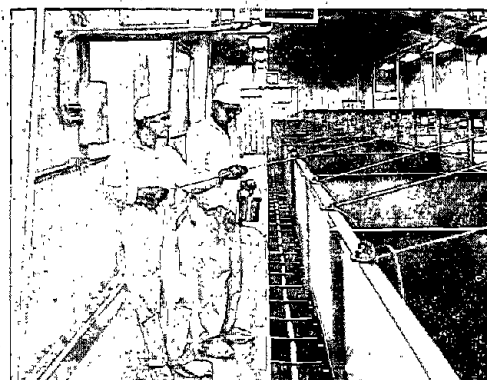


FIGURE 13.5. Plan of the Hanford experiment on ^{90}Sr in miniature swine. (Redrawn from McClellan et al. 1962. Reprinted with permission of Pergamon Press, Elmsford, New York, copyright 1962.)

Besides general clinical effects, the development of hematopoietic effects, including myeloproliferative disorders, the development of bone and dental defects, farrowing performance, and fetal and neonatal changes were researched in depth. A picture of the laboratory facility developed for this experiment is shown as figure 13.6.

FIGURE 13.6. Laboratory facility at Hanford for housing miniature swine showing individual feeding compartments and ^{90}Sr pellets being fed. (From McClellan et al. 1962. Reprinted with permission of Pergamon Press, Elmsford, New York, copyright 1962.)



2. Radiostrontium Studies in Pygmy Goats

This relatively small experiment was done for a species comparison with the swine on the one hand and laboratory rats on the other. Differences in both metabolism and effects were noted.

3. Passage of Pairs of Elements Through Food Chains

This work began with studies involving the passage of ^{90}Sr and stable strontium from soil to plants and the effect thereon of calcium content of the soil. This led to animal research, largely with rats, in which dietary intakes of this pair of elements were manipulated and the subsequent skeletal deposition measured. It led to a difference of opinion on the significance and utility of the "Observed Ratio" (OR) between Harry Kornberg, manager of the biology operation at Hanford and Cyril Comar at UT-AEC Farm (see section III). As in most such arguments, the truth lay between the extremes.^(a) The question is important to all research involving closely related elements. The Hanford work proved clearly that discrimination can be influenced markedly by conditions such as time and the concentration of the base-line element.

The work went on to look briefly at a second pair of elements, ^{137}Cs and stable potassium (details in the next section).

4. Radionuclides in the Fetal and Juvenile Mammal

Throughout the Hanford studies, much attention was directed to the placental transfer and metabolism of many of the radionuclides found in fallout in the fetus and the neonate (chapter 8). Not discussed there and to be reviewed herein was the reproductive performance of animals in the large experiment with radiostrontium in swine and changes in metabolism of some of the important elements in fallout with advancing age of the animal.

5. Research with Plants

The very first annual report of what was then the Biology Section of the Radiological Sciences Department of the Hanford Works describes research on the uptake of strontium, yttrium, cesium, and iodine from solutions by plants. It was shown that uptake was linearly proportional to concentration up to toxic levels and could be influenced by pH and by adsorption of the radionuclides on the roots of the plants. This work not only triggered some of the ideas and research concerning the behavior of pairs of isotopes, but extended to toxic effects of ^{137}Cs on cellular development of plants and later to the solubilization of plutonium and other transuranic elements in natural soils. Of particular interest was the different behavior of ^{238}Pu as compared to ^{239}Pu .

6. Aquatic Biology and Marine Sciences

The aquatic program at Hanford did not concentrate any special research efforts on fallout radionuclides. Much work was already under way on the effluents from reactors, fuel reprocessing, and other nuclear facilities, and most of the

(a) Obviously, no lasting problems persisted, since many years later Harry Kornberg and Cyril Comar became close colleagues at the Electric Power Research Institute in Palo Alto, California.

results have already been described (chapter 11). They are, of course, applicable also to fallout. There was much work on measurement and assessment of fallout radionuclides in marine biota (chapters 11 and 12), which included not only Richland and Hanford, but the Arctic, the Pacific, and the Columbia River and its environs.

There were, in addition to the areas named above, a few experiments to check on specific points, such as the relationship of the half-life of ^{137}Cs to body weight in humans (Eberhardt 1967) and some incidental work on uptake of transuranic elements in plants (Price 1972, 1973).

E. Los Alamos Scientific Laboratory, Now Los Alamos National Laboratory^(a)

The research at Los Alamos had a very general orientation. Despite the consistent and important participation of senior Los Alamos scientists in sounding the alarm concerning potential biomedical effects of fallout and making measurements in humans, animals, and the environment (see chapter 12), no single program there can be earmarked as stimulated by the problems of fallout. The single exception might be the work with plants spearheaded by Eric Fowler. Yet, much of the Los Alamos research has direct applicability to metabolism of fallout radionuclides. For example, the series of papers prepared over several years by Chester Richmond, J. Furchner, and colleagues and entitled, "Comparative Metabolism of Radionuclides in Mammals," has such applicability. This series, including graphs of the results, appears in chapter 8 along with a plan for electronic processing and analysis of the metabolic data (Richmond et al. 1964).

There was work, described in the annual reports from Los Alamos, on the effects of temperature and of hydration on retention in mice of radionuclides of importance in fallout (Furchner, Drake, and Richmond 1964; Furchner, Richmond, and Drake 1964, 1965; Furchner and Richmond 1963; Furchner et al. 1965), metabolism of radiocesium in man (Richmond, London, and Furchner 1964), distribution of ^{137}Cs in mice and dogs after chronic administration (Furchner, Richmond, and Trafton 1963), the effect of environmental temperature on retention of cesium in mice (Furchner et al. 1965), the long-term retention of cobalt in rats (Richmond and London 1967), and the disposition of ^{137}Cs during potassium depletion (Furchner and Drake 1973). All of these bear on understanding the behavior of fallout radionuclides. There were, in addition, the large efforts on the hot particle problem described in chapter 9, the work on tritium described in chapter 10, the many managerial and measurement activities around the tests described in chapter 12, and important contributions to the therapeutic removal of radionuclides to be described in chapter 19. Of special importance to the Los Alamos research of this period was the annular liquid scintillation counter described by Woodward, Richmond, and Langham (1956). There were studies on the retention of radionuclides in man using "Humco I," the fourth scintillation counter (e.g., Richmond, Furchner, and Langham 1962).

(a) I am greatly indebted to Dr. Robert G. Thomas for making available to me a complete set of the H-Division reports, for preparing extracts, and for providing selected reprints.

F. University of California at Los Angeles^(a)

The University of California at Los Angeles (UCLA) Project, except for its medical and nuclear medicine activities and some basic radiobiology, was largely devoted to work concerned with nuclear weapons testing and fallout therefrom. We have already met much of their work in chapter 12. There were also many laboratory projects, which concerned preponderantly the movement of fallout-type radionuclides in soils and plants and the influence of many factors in the environment. Some was semifield research, but much was done under greenhouse conditions.

In later years, the UCLA group became involved with general modeling for environmental transport, including cycling of nuclides in the environment of a Utah dairy farm and other food-chain transport, but this was more observational than research. The research and documentation will appear in sections III and IV.

G. University of Rochester

Research at the University of Rochester with radionuclides concentrated on alpha emitters such as polonium, plutonium, radon, and uranium, including chemical toxicity of uranium. As we saw in chapter 9, inhalation toxicology received much attention. In addition, the Rochester program considered long-term effects of external radiation, some of it pertinent to fallout problems. There was, of course, in addition, the ubiquitous graduate education program that covered all phases of radiation biology and toxicology.

There was a specific experimental foray into fission products and related radionuclides that concerned imbibed ^{90}Sr in monkeys and rats. This was done partly in response to the problems of fallout. The work with monkeys was similar to that at Berkeley, except for the route of administration. It was reviewed briefly in chapter 8. There was, in addition, detailed pathology done on the effects of ^{90}Sr in rats. Both experiments were sparked by Lawrence W. Tuttle, but the reports were produced largely by G. W. Casarett and colleagues. The findings will be included in the section on strontium in part IV of this chapter.

Della Rosa, Smith, and Stannard (1961) studied the renal clearance and behavior of strontium in the kidney and added a bit more detail to our knowledge of the mechanisms of discrimination for strontium over calcium at the point of excretion. This will be included in our general discussion of pairs of elements in section III.

Finally, the classic theoretical modeling done by H. A. Blair (chapter 8) had some pertinence to fallout radionuclides, especially plutonium, but was concerned as well with elements such as ^{226}Ra , ^{228}Ra , and ^{228}Th . The reader is referred to chapter 8 and the reference given therein for review of this facet of the Rochester contributions.

H. Lawrence Livermore Laboratory

We saw in chapter 12 that the Bio-Sciences Division of the Lawrence Livermore Laboratory (LLL) was developed primarily for research and assessment of the

(a) I am greatly indebted to Dr. E. M. Romney for making available to me a complete set of UCLA reports and the collected publications of the laboratory, for an illuminating interview and for selected copies and reprints.

problems of radioactive fallout. There was much work on aquatic systems and in the desert environment of NTS. The latter concerned primarily residual contamination with plutonium and will be considered in chapter 14. The aquatic biology work will be reviewed in section III.

I. Miscellaneous Other Operations

An interesting project pertinent to both aquatic biology and some of the radionuclides in fallout was carried out by Andrews and Warren (1969). Shields Warren, whom we have met at several points in this book, was interested in fisheries and aquatic biology, an interesting avocation for a pathologist. He operated on the premises of his summer cottage on Cape Cod, Massachusetts, an enterprise known as "Sea Farm Research Foundation." Andrews spent a summer there with fresh live clams and quahogs and measured their ability to concentrate ^{131}I , ^{85}Sr , and ^{59}Fe from sea water and to pass them on to the environment in feces. There were real differences between the two species as well as clear indications that the processes involved may be important for transfer of nuclides to bottom sediments. (More later.)

The work at the University of Washington Fisheries Laboratory, at the Woods Hole Oceanographic Institution, the School of Oceanography of Oregon State University, at the Puerto Rico Center, and at the Scripps Institution of Oceanography included many laboratory experiments directly related to fallout problems. Since we have already reviewed these programs in some detail in chapters 11 and 12, we will refrain from further description here, except to cite the experiments as appropriate in the following sections.^(a)

Work abroad was quite pertinent to the subject of this chapter. It will be reviewed briefly at the chapter's conclusion.

III. Selected Research Areas

We will consider now some of the results of research in the several laboratories described in sections I and II. Three major areas are chosen for review in this section: the metabolism of pairs of elements, i.e., a radioactive nuclide and its chemical congener, stable or radioactive; plants and soil-plant interrelationships; and findings in aquatic biology. In section IV, we will review the results collected together for the most important radionuclides in fallout. Work in the United States will be emphasized.

The period of greatest activity occurred in the late 1950s and 1960s, and we will concentrate on these years. Some of the work continued into later years, but it could no longer be called research stimulated by the problems of fallout.

A. Metabolism of Pairs of Elements— The Observed Ratio and Discrimination Factors

1. The Concept

When we considered the measurement of fallout in the environment in chapter 12, we were introduced to the idea of reporting the data for radionuclides

(a) A broad review of the entire problem of ecologic effects from radioactive emissions from nuclear power plants has been prepared by Rice and Baptist (1974). This includes reference to experimental work done at many installations named above.

such as strontium and cesium that had chemical properties very similar to elements already present in the environment, i.e., calcium and potassium in terms of the ratio of these two.^(a) We met the Strontium Unit (née "Sunshine Unit") which was defined as 1 pci (i.e., 1 μ ci) of ^{90}Sr per gram of calcium. Since the radioactive isotope was always present in gravimetrically very small quantities, it was logical to assume that its behavior would follow qualitatively and quantitatively that of its congener, calcium. The practice of using the ratio of the elements was followed quite faithfully in the early days of fallout reporting. Yet, there were many misgivings about its universal applicability and a strong stimulus was present to mount experimental research around this important concept and the biological mechanisms responsible. Particular emphasis was placed on dietary contamination and how to estimate concentrations in humans from those in the environment.

In the midfifties, Comar, Wasserman, and Nold (1956) presented a concept they expressed as the "Strontium-Calcium Observed Ratio." They also denoted the difference in behavior of strontium and calcium at various steps in the food chain as the "Strontium-Calcium Discrimination Factor." These were given acronyms of "OR" and "DF," respectively, and were generalized to any situation concerned with pairs of elements.

For strontium the OR was defined as:

$$\text{OR}_{\text{Sample-precursor}} = \frac{\text{Sr/Ca of sample}}{\text{Sr/Ca of precursor}}$$

Further, the OR was considered to be determined by the sum of the discrimination processes at the several steps, i.e.:

$$\text{OR} = (\text{DF}_1) (\text{DF}_2) (\text{DF}_3) \dots (\text{DF}_N)$$

The logic and some examples were given in this initial description. An eloquent and persuasive version of the logic was presented by Comar and Wasserman at the first major symposium on radioisotopes in the biosphere at the University of Minnesota (Comar and Wasserman 1960). Let us read the logic and application in their own words:

As early as 1958 there was an intuitive feeling that we should develop more data about the behavior of the "bone-seeking" fission products in the food chain, even though there was no recognition of the fallout problem as we now see it. Attention was soon focused on radiostrontium, and much work was done on the behavior of this radioisotope by itself in laboratory and domestic animals. As a matter of experience, often bitter, it is recognized that the behavior of any one substance in a biological system is often interrelated with other parameters that must eventually be taken into account. Accordingly, attention was turned to the comparative behavior and interrelations of strontium and calcium under normal nutritional situations as a beginning.

The early work of Pecher [and Pecher] (1941) had shown the similarities in behavior of strontium and calcium. Numerous studies thereafter showed that substances which modified calcium behavior also modified strontium behavior in a similar way (vitamin D, parathormone, lactose).

It appeared to some that the behavior of radiostrontium in the food chain was inevitably linked with the behavior of calcium. Furthermore, it seemed that to try to determine the behavior of radiostrontium in the animal or human population

(a) These were termed congeners.

without taking advantage of the long, hard lessons learned of calcium behavior was indeed wasteful of the experiences of others. As a specific example: We know that in the mature individual there is no net retention of ingested calcium—we would therefore expect no net retention of ingested radiostrontium under steady state conditions after the skeleton has been labeled; observations bear this out (Harrison et al. 1955). How then does one predict the radiostrontium level in the skeleton from knowledge of the intake? And how does one determine the radiostrontium concentration in the newly-forming areas of bone from knowledge of the intake? There seemed little question that the information needed—namely the relationship between radiostrontium in the diet and in the human population—is to be obtained with much more certainty by consideration of strontium-calcium behavior than by consideration of strontium behavior alone.

(Comar and Wasserman 1960, p. 526)

Practical use of observed ratios:

The practical use of an Observed Ratio for prediction purposes depends primarily upon whether a given value or range of values is generally valid. A comment may then be in order as to the variability that might be expected in the differential behavior of strontium and calcium in the mammal.

Examination of data obtained by independent methods in many laboratories and many countries has indicated that under usual dietary conditions the OR values fall within a reasonably narrow range, with few indications of variations as high as a factor of two. There appears to the authors a remarkable constancy, especially for dealing with populations and with considerations that contain uncertainties of much higher order.

It is recognized, and, as a matter of fact, early pointed out by the authors, that the OR values can be changed by unusual dietary modifications. Also, it was shown that in very early life, rats have less discrimination against strontium; the differences were small in later life (Comar et al. 1957). These limitations must always be borne in mind and OR values used only when they can provide some advantage.

(Comar and Wasserman 1960, p. 531)

And still later:

For radiostrontium, it appears that consideration of strontium-calcium ratios is of much greater usefulness than consideration of strontium retention alone. The reasons can be summarized: (a) There appears to be a reasonably constant relationship under normal dietary conditions between strontium-calcium ratios in diet and those in the body or milk; (b) The strontium-calcium ratio predicted in the body at any given time will reflect the radiocontamination at the local areas in bone that are active at the time; (c) Radiostrontium retentions will vary greatly with age, diet, and other factors; in mature individuals retention will progressively decrease to zero as the skeleton becomes labeled under constant intake; calcium retentions would be expected to be parallel; (d) The behavior of radiostrontium ingested will be related to the calcium intake; (e) The calcium level of the body is reasonably constant regardless of dietary intake under adequate or optimal conditions; the calcium of blood is under close homeostatic control and tissues are similar in calcium content. This behavior of calcium makes it a good standard of reference; (f) Calcium metabolism and nutrition have been widely studied in the past.

For radiocesium there apparently is not the close relationship with potassium as has been observed for strontium-calcium. Much more data are required for an understanding of cesium behavior and the effects of the important parameters.

(Comar and Wasserman 1960, p. 539)(a)

(a) References given in the above quotations have been added to the bibliography for this chapter.

Much research was done to determine: (1) whether or not the OR was indeed reasonably constant and thus useful to the degree implied above, (2) the differential behavior of calcium and strontium in physiological processes, and (3) their possible mechanisms. We will consider these in turn.

2. Is the Observed Ratio for Strontium/Calcium Reasonably Constant?

Some examples of strontium-calcium observed ratios in animals for the process diet-to-bone are shown in table 13.2A and B, which is taken from Comar and Wasserman (1960), who in turn obtained it from one of the early United Nations (UNSCEAR) reports. Similar figures, but concerning diet to milk, are shown in table 13.3.

TABLE 13.2A. Strontium-Calcium Observed Ratios in Animals; Diet to Bone

Species	Diet	Method	Remarks	OR Value
Cow	normal	dbbl. tracer	8 animals	0.21
Goat	normal	dbbl. tracer,	2 animals	0.23
		daily dose		
Sheep	grass	stable Sr/Ca	6 animals	0.24
		ratios		(0.15-0.31)
Sheep	grass	Sr ⁹⁰ /Ca ratios	6 animals	0.23
				(0.09-0.42)
Rat	milk	dbbl. tracer		0.57
Rat	non-milk	dbbl. tracer		0.27
Rat	non-milk	lifetime feeding		0.28
		of Sr ⁹⁰ /Ca		
Rat	non-milk	stable Sr/Ca		0.27
		ratios		
Rats and rabbits on desert				0.14-0.22

TABLE 13.2B. Strontium-Calcium Observed Ratios in Man; Diet to Bone

Diet	Method	Remarks	OR Value
Milk	dbbl. tracer with	4 patients, 9	0.54
	each meal	to 73 yr. old	(0.50-0.62)
Normal mixed	stable Sr/Ca in	avg. U. K. adult	0.25
	diet and bone	diet	
Normal mixed	stable Sr/Ca in	avg. Canadian	0.5
	diet and bone	diet	
Normal mixed	stable Sr/Ca in	1 normal	0.24
	diet and bone		
Non-milk	dbbl. tracer with	4 patients	0.44
	each meal		(0.37-0.51)
Non-milk	dbbl. tracer,	2 patients	0.35
	single dose		(0.25, 0.45)
Normal mixed	Sr ⁹⁰ /Ca in diet	Indirect	0.25
	and bone	calculation	

Source: Reset from Comar and Wasserman 1960 who obtained the data from the UNSCEAR report of 1958. Reprinted with permission of the University of Minnesota-Twin Cities, Minneapolis, Minnesota, copyright 1960.

TABLE 13.3. Strontium-Calcium Observed Ratios in Lactating Animals; Diet to Milk

Species	Method	OR value
Cow	Sr and Ca at different times	0.14
Cow	Sr ⁹⁰ /Ca in U.S. surveys	0.16
Cow	Sr ⁹⁰ /Ca in U.K. surveys	0.09
Cow	Stable Sr/Ca ratios in U.S.	0.12
Goat	Dbbl. tracer daily	0.09

Source: Modified slightly from Comar and Wasserman 1960 who obtained the data from the 1958 UNSCEAR report. Reprinted with permission of the University of Minnesota-Twin Cities, Minneapolis, Minnesota, copyright 1960.

These values do indeed look reasonably constant considering the chances for variability in such systems. Note, however, that the OR for diet to bone in man appears to be higher in general, although probably not statistically significantly higher, than in animals. Note also that the OR for diet to milk is lower in lactating animals than from diet to bone, which reflects a fairly general finding, viz., the OR values for different physiological processes are not the same. For example, in the rat, when considering placental discrimination, the OR from diet to mother was 0.28, from fetus to diet 0.17, from mother to urine 4.7, and from fetus to mother 0.71.

In the lactating goat, the OR from diet to milk was 0.09, from diet to plasma 0.23, from plasma to milk 0.40, from plasma to urine 16, and from diet to urine 4 (Comar and Wasserman 1960, p. 530). These differences reside in the different discrimination processes involved.

An important test of the practical constancy of the OR for strontium/calcium would be the effect of variations in the calcium or strontium intake using either stable or radioactive isotopes. Comar and Wasserman (1960) report OR values for a number of processes in the lactating cow and the lactating goat on diets with varying calcium or stable strontium content. The calcium intake was varied from about one-half the normal to three times the normal level starting three weeks before the experiment. As shown in table 13.4A and B, the OR values were satisfactorily alike, particularly the OR_{milk-diet}.

Further investigation, particularly at Hanford, indicated that the relationships were sometimes far from a strict proportionality. Verbatim application of the philosophy behind the use of OR for hazard evaluation, for example, predicts that bone deposition of radiocalcium or radiostrontium should be inversely proportional to the dietary calcium level. At the Minneapolis symposium we have been quoting, Roy Thompson from Hanford presented data gathered by Ray Palmer and his associates, also at Hanford, on the buildup of ⁴⁵Ca and ⁹⁰Sr in rat bone during periods of chronic feeding of diets with calcium contents ranging from 0.03% to 2.0% (Thompson 1960). There was the expected effect qualitatively, less bone deposition of both ⁴⁵Ca and ⁹⁰Sr as the dietary calcium increased. However, the relationship was not an inverse proportionality. Whereas the dietary calcium covered a sixty-seven-fold range, the change in radiocalcium deposition was only sixteenfold and that of radiostrontium only fourfold. This is not surprising, if one considers that the bone deposition can only be related to blood calcium and not directly to that in the diet. The deposition of ⁴⁵Ca in bone turned out to be essentially proportional to the levels of ⁴⁵Ca in

TABLE 13.4A. OR Values in the Lactating Cow

Treatment	Cow No.	OR _{plasma-diet}	OR _{urine-diet}	OR _{urine-plasma}	OR _{feces-diet}	OR _{milk-diet}
Low calcium	3	0.17	2.2	13.	1.2	0.084
	10	0.18	0.67	3.7	1.7	0.12
	Mean	0.18	1.4	8.4	1.4	0.10
Normal calcium	5	0.20	1.2	6.2	1.2	0.10
	8	0.15	1.0	6.7	1.3	0.083
	Mean	0.18	1.1	6.4	1.2	0.092
High calcium	4	0.10	5.1	51.	1.3	0.072
	6	0.16	1.2	7.3	1.2	0.14
	Mean	0.13	3.2	29.	1.2	0.11
High strontium	7	0.24	0.54	2.2	1.1	0.11
	9	0.18	0.77	4.3	1.5	0.13
	Mean	0.21	0.66	3.2	1.3	0.12

TABLE 13.4B. OR Values in the Lactating Goat

Treatment	Goat No.	OR _{plasma-diet}	OR _{urine-diet}	OR _{urine-plasma}	OR _{feces-diet}	OR _{milk-diet}
Low calcium	3	0.25	3.1	13.	1.3	0.11
	6	0.22	3.4	15.	1.2	0.12
	Mean	0.24	3.2	14.	1.2	0.12
Normal calcium	7	0.23	1.3	5.5	1.3	0.11
	10	0.27	1.1	4.2	1.0	0.13
	Mean	0.25	1.2	4.8	1.2	0.12
High calcium	4	0.29	0.98	3.4	1.1	0.13
	5	0.32	0.49	2.0	1.2	0.10
	Mean	0.31	0.74	2.7	1.2	0.12
High strontium	8	0.37	0.82	2.2	1.3	0.11
	9	0.32	0.89	2.8	1.2	0.14
	Mean	0.34	0.86	2.5	1.2	0.12

Source: Reset from Comar and Wasserman 1960. Reprinted with permission of the University of Minnesota-Twin Cities, Minneapolis, Minnesota, copyright 1960.

blood. As Thompson remarks, "The bone simply isn't aware of the dietary calcium level. It sees only the calcium in the blood . . ." (Thompson 1960, p. 519).

The variations in the $OR_{\text{bone-diet}}$ as a function of both the calcium intake level and of time in the experiment are shown in figure 13.7. Obviously, a range from an OR of about 0.47 on a high calcium diet at one day to about 0.08 on a low calcium diet at one hundred days, the extremes seen in the figure, could have a large effect on the usefulness of the OR if applied uncritically for hazard evaluation.

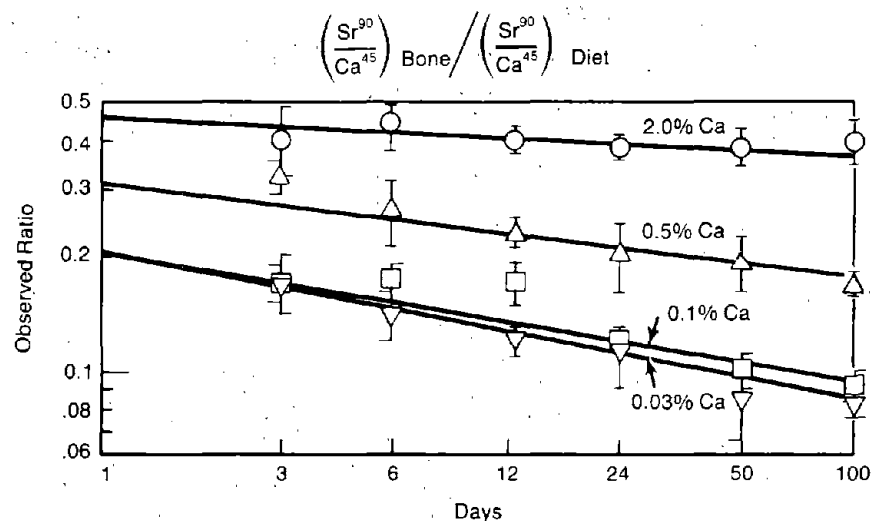


FIGURE 13.7. Observed Ratio (bone-diet) during period of chronic feeding of diets of various total calcium content to rats. (Modified slightly from Thompson 1960. Experiment of Palmer and colleagues at Hanford. Reprinted with permission of the University of Minnesota-Twin Cities, Minneapolis, Minnesota, copyright 1960.)

A view of a chronic feeding experiment at Hanford carried from weaning to two hundred days in rats is seen in figure 13.8A and B. Although the spread in figures is rather large, and the ranges overlap, the difference between 0.1% calcium and 0.5% calcium in the diet appears large. Why the 2% calcium diet should produce OR values between these two is not clear.

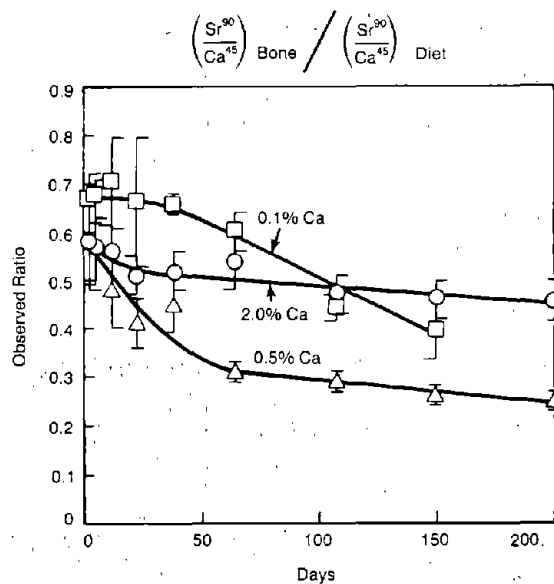


FIGURE 13.8A. Observed Ratio (bone-diet) in rats fed from weaning on ^{90}Sr - and ^{45}Ca -labeled diets of various total calcium contents. (Redrawn from Thompson 1960, using data of Palmer, Thompson, and Kornberg 1958. Reprinted with permission of the University of Minnesota-Twin Cities, Minneapolis, Minnesota, copyright 1960.)

FIGURE 13.8B. The same data as in figure 13.8A plotted with shading for the ranges. (Redrawn from Kornberg 1960. Reprinted with permission of the University of Minnesota-Twin Cities, Minneapolis, Minnesota, copyright 1960.)

Further consideration of the lack of inverse proportionality between dietary calcium and deposition of ^{45}Ca or ^{90}Sr is pictured in figure 13.9, taken from a discourse by Harry Kornberg from Hanford.^(a) Note here that the ordinate is not OR. Yet, the lack of linearity is clear as well as the moderately large standard deviations. As stated, straight lines should have resulted if strontium and calcium have a linear inverse relationship.

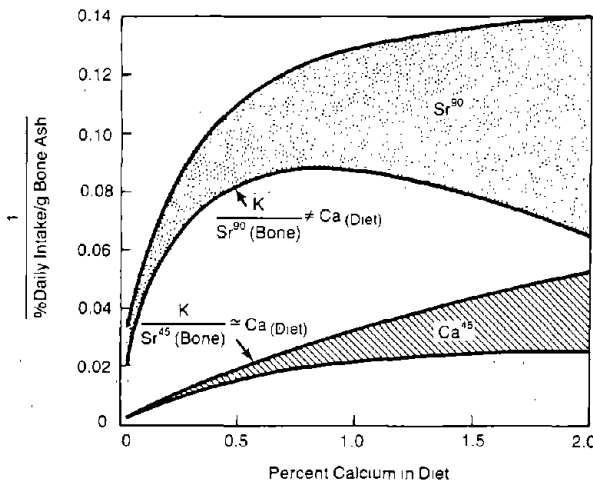
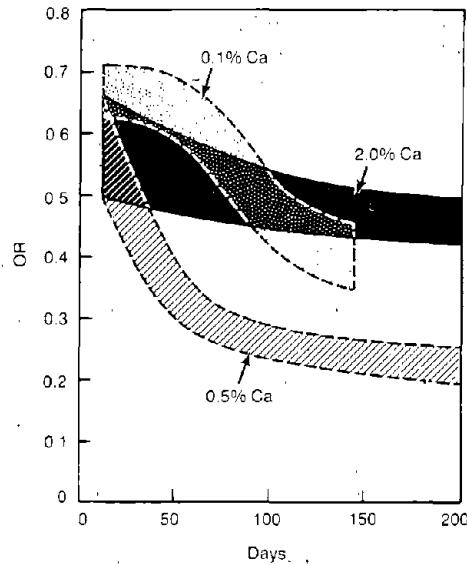
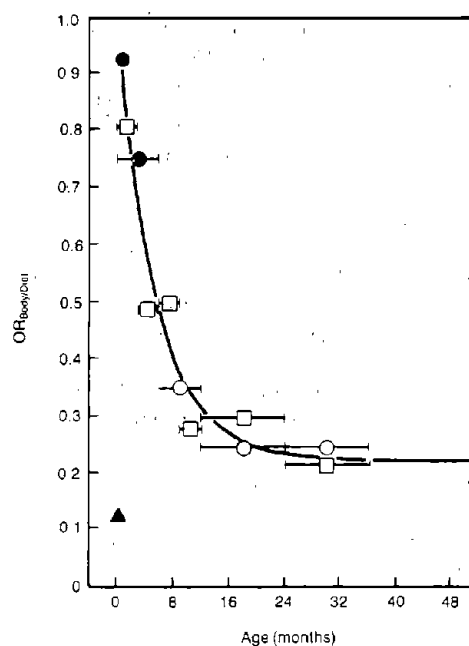


FIGURE 13.9. Effect of dietary calcium on skeletal deposition of Sr^{90} in rats. Straight lines should have resulted if strontium and calcium have a linear inverse relationship to each other (width of lines is proportional to standard deviations). (Kornberg 1960, using data from Palmer 1958. Reprinted with permission of the University of Minnesota-Twin Cities, Minneapolis, Minnesota, copyright 1960.)

As we will see in a following section, the discrimination mechanisms underlying the OR are not fully developed in the very young. Thus, age can influence the OR. In an erudite review concentrating on mechanisms, Comar (1967) presents a summary of $\text{OR}_{\text{body-diet}}$ in young children as related to age and gives a single point for the $\text{OR}_{\text{body-mother's diet}}$ in a newborn. These vary from nearly 1 in the very young to the usual value seen in adults of between 0.2 and 0.3 beginning at about sixteen months of age. These are full balance studies and are shown in figure 13.10.

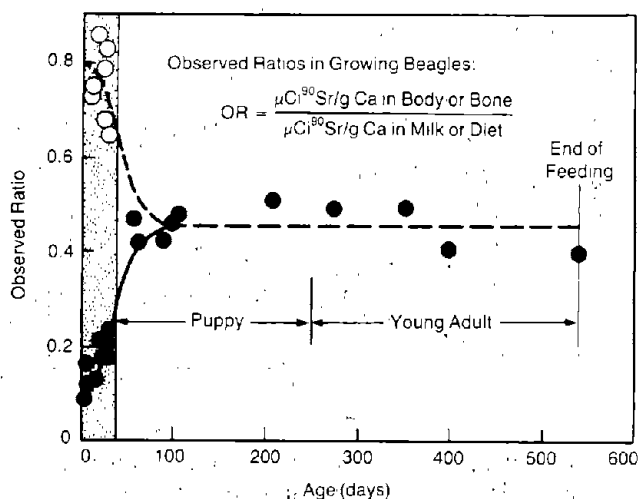
(a) See also figure 13.8B.

FIGURE 13.10. $OR_{body/diet}$ as related to age of young children. \circ , Beninson, Migliori, and Ramos (1964), ^{90}Sr ; \square , Beninson, Migliori, and Ramos (1964), Sr ; \bullet , Lough, Rivera, and Comar (1963), ^{90}Sr ; Δ , Comar (1967), New-born, $OR_{body/mother's\ diet}$. The references given in this legend have been placed in the bibliography. (Redrawn from Comar 1967 and reprinted with permission of Academic Press, New York, copyright 1967.)



An illustration of the behavior of the observed ratio of strontium to calcium in growing beagles is shown in figure 13.11, which comes from the large experiment at the University of California at Davis (see section I).

FIGURE 13.11. Observed Ratio as a function of age in beagles. The dotted area on the left represents suckling: broken lines, pup body/milk; continuous line, pup body/maternal diet. Discrimination is low for the first 30 days or so but reaches a more or less constant and higher figure by 100 days. The lower solid line represents the OR from the pup body versus the maternal diet and has interposed the factors



for gut uptake etc., by the mother as well as the factors in the pup represented by the broken line. (Redrawn from Goldman and Della Rosa 1967. Reprinted with permission of Academic Press, New York, copyright 1967.)

It is clear from the experimental work quoted that the OR for strontium versus calcium is hardly a rigid constant, that it can be varied by such factors as age and the dietary intake of calcium or stable strontium. Yet, the ratio is sufficiently

constant under the conditions of most interest to be useful. Any problems with its application may arise from failure to take cognizance of the necessary caveats. Comar, Russell, and Wasserman (1957) emphasize the care needed to ensure that the ratios measured truly represent the quantities available to the organism.

It is at the first step, soil to plant, that the largest source of error may occur in calculation of the overall OR. This was the source of Kornberg's concerns for the usefulness of the OR concept as indicated earlier (section II). The preamble to Kornberg's dissertation on the subject is given below.

As often happens in research, we began a series of investigations after making some observations that seemed to be at odds with common sense. For example, it seems common sense to say that if a plant takes up 10 Sr^{90} atoms per second from the soil, then if we add to the soil 9 inert strontium atoms for each Sr^{90} atom there, the plant should now take up only 1 Sr^{90} atom per second. But when essentially such an experiment was done by Rediske, Cline, and Selders (1955), the results did not bear this out. Instead, the same number of Sr^{90} atoms went up the plant, regardless of the number of inert strontium atoms that were present in the root environment.

Such a result may seem odd until one thinks in terms of basic mechanisms. It is not that the plant insists on taking up 10 Sr^{90} atoms per second, regardless of inert strontium atoms present. Instead, the rate governing process in this case seems to be the flow of solution up the plant. Under such conditions it does not matter what solutes are present along with the Sr^{90} .

Cline and Hungate (1956) obtained similar results when calcium atoms were used to dilute Sr^{90} atoms in soil. Again the uptake of Sr^{90} was not depressed by increasing soil calcium. It was about at this time that public interest in the hazards of fallout became widespread, and it was popularly asserted that the hazard of Sr^{90} was inversely proportional to the concentration of calcium in the environment. This, of course, was quite contrary to our results, at least in plants. The difference between what we read in the papers and what we saw in the laboratory started us attempting to find which was right.

Before long Hungate, Uhler, and Cline (1958) found that calcium could, indeed, depress the uptake of Sr^{90} into plants. However, this occurred only in acidic soils low in calcium. But even here we did not observe a linear inverse relationship in depression of Sr^{90} uptake with increase of calcium. Fredrikson et al. (1958) observed similar effects and pointed out that the uptake of Sr^{90} into plants is not inversely proportional to soil calcium.

(Kornberg 1960, pp. 255-256)^(a)

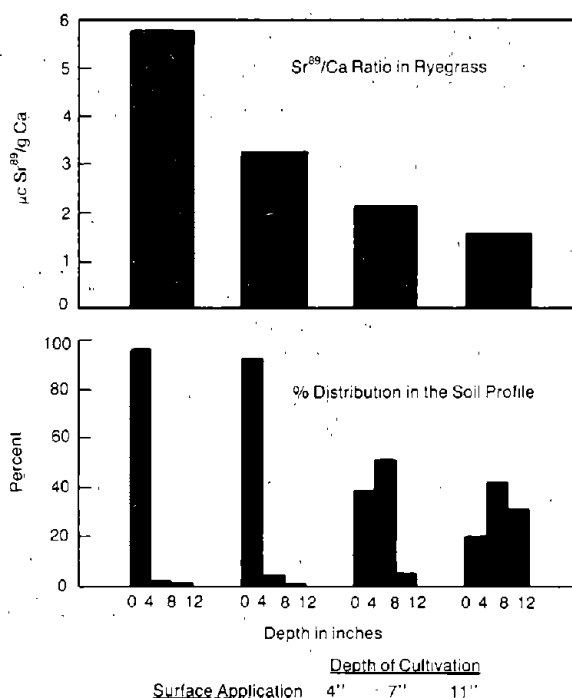
This plant work was the impetus for the work with rats at Hanford already discussed.

Kornberg also shows work done by Uhler (1959) where bean plants were grown in nutrient cultures containing ^{85}Sr , ^{45}Ca , and different concentrations of stable calcium to see what effect calcium concentration would have on the strontium/calcium ratio within the plants. There was a marked effect in roots, less marked in stems, and essentially no effect in leaves. Thus, it appeared that the plant did not discriminate either for or against strontium in the transfer of the strontium-calcium pair to the leaves that are the components most likely to become forage for cattle.

(a) References in the above quotation have been added to the bibliography for this chapter.

There are many problems under practical conditions. Radiostrontium is unlikely to be homogeneously mixed throughout the soil. In fact, great care must be taken to ensure proper mixing for any laboratory experiment. There is no way to express the strontium/calcium of the nutrients to which the roots themselves are exposed under most field growth conditions. If the soil is not cultivated, the strontium will tend to reside primarily in the upper layers and move downward slowly with time. Cultivation can, of course, hasten the mixing. Russell (1960) discusses work by Milbourn, Russell, and Ellis (1959) showing the ratio of $^{89}\text{Sr}/\text{g Ca}$ in ryegrass and also the extent of mixing of the ^{89}Sr in the soil profile as a function of depth of cultivation. The results are shown in figure 13.12.

FIGURE 13.12. Distribution of Sr^{90} in the soil profile and ratio of Sr^{90} to calcium in ryegrass grown on land which was either contaminated on the surface or to varying depths by cultivation before the sowing of crops. (Redrawn from Russell 1960 taken from data of Milbourn, Russell, and Ellis 1959. Reprinted with permission of the University of Minnesota-Twin Cities, Minneapolis, Minnesota, copyright 1959, 1960.)

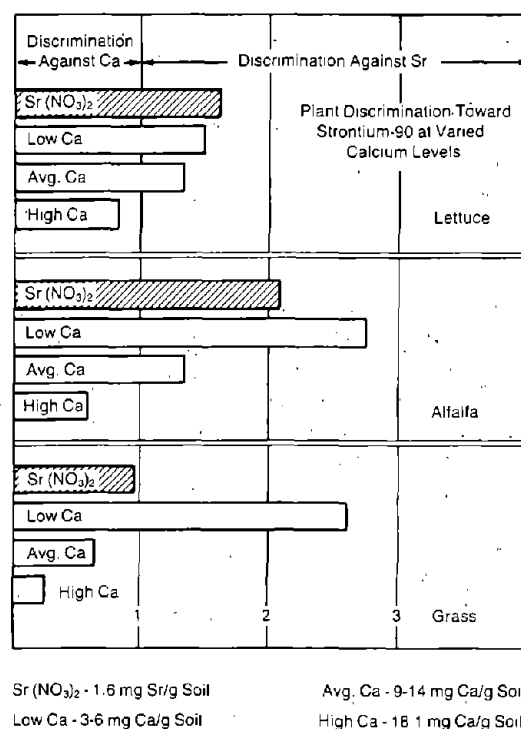


It is clear, as one might surmise intuitively, that an OR involving soil-to-plant interactions could be sadly misleading if either the soil were not mixed or the concentrations seen by the roots were not the ones measured. This is a significant difference between laboratory and field conditions. In the laboratory, with strontium well mixed with the soil, the observed ratio seems to vary within narrow limits over a wide range of concentrations of calcium in soil (see Fredrikson et al. [1958] as well as research mentioned earlier), and in general seems to be nearer to unity than the OR values for such processes as bone to diet, etc.

Another factor, mentioned by Eisenbud (1973, p. 130), is that a portion of the radiostrontium in the soil may become unavailable to plants as a result of chemical reactions in the soil.

Even though the discrimination factor between plant and soil tends toward unity more than that of other processes, it should not be concluded that this always applies, even under the best of laboratory conditions. An example of the variations possible under varying conditions of calcium content of the soil and for different plants in a good laboratory experiment is shown in figure 13.13, taken from Adams, Christenson, and Fowler (1965) from Los Alamos.

FIGURE 13.13. Plant discrimination toward ^{90}Sr at varied calcium levels. (Redrawn from Adams, Christenson, and Fowler 1965. Reprinted with permission of Elsevier Science Publishers, Amsterdam, copyright 1965.)



It should be noted that discrimination is toward strontium at low calcium and against strontium at high calcium, even though there is indeed little discrimination either way at average calcium with the exception of grass.

Results of a similar nature can be found in extensive work at UCLA using barley, buckwheat, cow peas, some grains, and some vegetables (Nishita, Romney, and Larson 1965). We will review the actual experiments briefly in a following section.

What can we conclude from the above? Clearly the OR concept has utility when used correctly. Wasserman (1960) concludes:

Although the observed ratio (OR) may be confusing to the uninitiated, it certainly is the only rational method for calculating the differential movement of two similar ions from one physiological compartment to another. If an atom ratio for Sr/Ca in a product compartment is observed to be 1/10, this ratio will only have meaning in terms of comparing the movement of calcium and strontium across boundaries if the atom ratio of Sr/Ca in the precursor compartment is known. The observed ratio merely formalizes this relationship where, by definition, the OR is the Sr/Ca ratio in the product compartment (e.g., skeleton) relative to the atom ratio of Sr/Ca in the precursor compartment (e.g., diet). Using the observed ratio as defined, the comparative movement of calcium and strontium in gastrointestinal absorption, urinary excretion, kidney clearance, placental transfer, and mammary transfer can be readily calculated from suitable observations. (Wasserman 1960, pp. 568-569)

In contrast, Kornberg was impressed by the lack of inverse proportionality and the variability of the OR and felt that these limited its usefulness for hazard assessment. He wondered if more conventional units might not do as well. He was impressed, however, by the contributions the concept of the ratios can make to fundamental biology.

Thompson took the view that the ratio approach simplifies the problems of hazard evaluation but that those primarily concerned with biological

mechanisms may be more impressed by the differences in the behavior of the ions than the similarities!

3. Other Pairs of Elements

Much research was done in several of the laboratories discussed in sections I and II on the behavior of cesium versus potassium. We saw in chapter 12 that the fallout-generated ^{137}Cs in inhabitants of Jamaica was higher than in persons from many other areas, apparently because the soil of the region was low in potassium.

Cesium is quite firmly bound in soils, which has the effect of indicating heavy "discrimination" by plants against cesium. It is not physiological discrimination. Langham and Anderson (1959) cite work of Auerbach (1957) at Oak Ridge showing that corn grown in the White Oak Lake bed (chapter 11) had a $^{137}\text{Cs}/\text{K}$ ratio of only 0.01 of the exchangeable $^{137}\text{Cs}/\text{K}$ in the soil. Also, Menzel (1954) reported a "discrimination factor" of 0.04 in the $^{137}\text{Cs}/\text{K}$ ratio of barley and corn versus the ratio in the soil. This type of "discrimination" is, of course, mechanistically quite different from the strontium/calcium discrimination we have been considering, since it involves the chemical state of the material to be absorbed, not the processes of absorption.

There was some effect of potassium concentration. Menzel (1954) showed that plant uptake of ^{137}Cs was inversely proportional to exchangeable soil potassium. However, with 75% or more of the cesium in the soil unavailable to plants, any changes in cesium behavior caused by potassium concentration are bound to have a relatively small effect overall. Also, an observed ratio for cesium/potassium could be meaningless unless it referred only to the mobile forms of cesium and potassium.

The situation in animal processes is somewhat more regular but not qualitatively different. The ^{137}Cs is readily transferred from diet to milk in the lactating mammal with a cesium/potassium ratio of about 1.4 in both cow and goat. This is interpreted as indicating little, or at least only slight, selection. There was something resembling an inverse ratio of cesium and potassium in animal tissues, but these seemed to apply mostly to situations with deficient diets.^(a) The observed ratio $^{137}\text{Cs}/\text{K}$ for muscle versus diet was not a constant (Wasserman et al. 1965). The value of

$$\frac{^{137}\text{Cs}/\text{K muscle}}{^{137}\text{Cs}/\text{K diet}}$$

ranged from 1.0 to 5.3 when the level of dietary potassium ranged from 0.2% to 1.8%. Comar and Wasserman (1960) found that the $^{137}\text{Cs}/^{42}\text{K}$ ratio also varied considerably among tissues in the same animal, i.e., 0.3 to 3.7 and, in the lactating goat, at least, it did not correlate with the total potassium content of the tissues. A ninefold difference in dietary potassium caused only a twofold difference in the ^{137}Cs concentration of muscle (Wasserman 1960). It appears that cesium and potassium behave relatively independently of each other, and their movements in the body are competitive to only a small degree.

(a) The people at the UT-AEC Farm (Mraz and Patrick 1957) found that increased dietary potassium decreased the retention of ^{137}Cs only when the animal was in potassium deficiency. If adequate levels of dietary potassium were already present, further increase had no effect on the retention of radiocesium.

Despite these facts, some practical use can and has been made of the cesium/potassium ratio, particularly for environmental contamination.^(a) On the basis of an extensive survey of cesium in milk and other foods, the Los Alamos group (Langham and Anderson 1959) decided that an average discrimination factor of about two against potassium existed in the passage of cesium from diet to the tissues of humans. As indicated in figure 13.14, an overall OR for both plant and animal sources can be determined as $0.5 (0.01 \times 2 \times 2) + 0.5 (0.01 \times 2) = 0.03$, assuming that about half of the dietary potassium comes from plants and half from animal sources and that the step from soil to plant has an OR of 0.01.

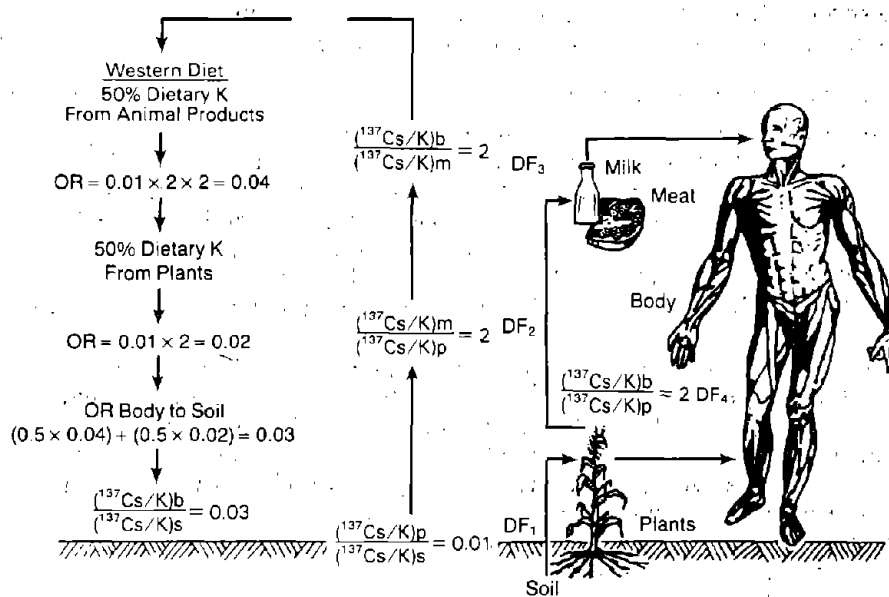


FIGURE 13.14. Ecological discrimination against Cs^{137} with respect to potassium (U.S. population). The subnumerals in the figure are: b = body, p = plant, m = milk and s = soil. (Redrawn from Langham and Anderson 1959. Reprinted with permission of Pergamon Press, Elmsford, New York, copyright 1959. See also Langham 1965.)

There were theoretical reasons to expect rubidium and potassium to behave as a pair; in fact, rubidium is sometimes substituted for potassium in tracer studies. Some examples of rubidium-potassium discrimination in plants are referenced in Nishita, Romney, and Larson (1965). We will not follow these further since rubidium is not important among the fission products. Ruthenium (e.g., ^{106}Ru) is important and does distribute differently in different tissues, but this is not because it is paired with anything else.

Special cases of paired behavior for different isotopes of the same element have been the subject of many investigations. The best examples are seen with isotopes of iodine and plutonium.

(a) This will be considered in more detail in part 6 of this section.

It has become well established that longer-lived iodine isotopes (e.g., ^{131}I) seem to be less effective per rad of absorbed dose compared to shorter-lived isotopes such as ^{132}I , ^{133}I , and ^{135}I and low-LET external x- or gamma-radiation. The factor has been placed as high as twenty but in recent years has been reduced to ten and very recently has been conservatively placed at three for long-term effects in man (NCRP 1985). This difference may reside in relative specific activities.

The difference in both behavior and effectiveness of ^{238}Pu versus ^{239}Pu clearly resides in difference in specific activities with, for example, much more radiolysis of the medium and the various colloidal complexes of plutonium in the case of the shorter-lived ^{238}Pu . Neither of these involves discrimination of the type discussed above, but the end result can be comparable.

4. Discrimination Factors

If there is no selective metabolism or transfer of one element of a pair over another, the OR as defined in the previous section would be unity. The fact that it is frequently not unity means that there is differential handling either for or against one element over the other. Comar, Wasserman, and Nold (1956) called these processes "discrimination," as we have already seen, and the measure of it a "discrimination factor" (DF).^(a) For a pair like strontium-calcium, the DF is conceptually the inverse of the OR. This was followed up in humans by Comar, Russell, and Wasserman (1957).

Much effort was expended in determining discrimination between strontium and calcium at each major step in the food chain. As indicated above, the factor between soil and plant for strontium-calcium was small enough and uncertain enough (partly because of incomplete mixing of the radiostrontium with soil) to be considered as unity. However, for absorption from the gut, excretion in the urine, secretion into milk, and placental transfer, there was clear evidence for discrimination. It was always for calcium and against strontium if one defines "for" and "against" as in the direction most favorable for having the minimal body or bone burden of radiostrontium. In simple terms, the absorptive and urinary discrimination can be represented by:

$$\begin{aligned} \text{DF}_{\text{absorptive}} &= \frac{100 - \% \text{ radiostrontium in feces}}{100 - \% \text{ radiocalcium in feces}} \\ \text{DF}_{\text{urinary}} &= \frac{\text{OR}_{\text{retained - diet}}}{\text{DF}_{\text{absorptive}}} \end{aligned}$$

Some early quantitative values for these are shown in table 13.5, taken from the landmark paper by Comar, Wasserman, and Nold (1956). Immediately apparent from this table is the fact that discrimination against strontium is greater for absorption from the gut than for urinary excretion and that diet can influence the absorptive discrimination markedly.

In pregnant rats, it was clear (Wasserman et al. 1957) that placental discrimination occurred against strontium such that the $\text{DF}_{\text{placenta-fetus}} = 0.65$. Absorptive and urinary discrimination factors in the pregnant rat were 0.42 and 0.63, respectively. The phenomenon was confirmed qualitatively in other species.

(a) The idea was already in use in many areas of mineral metabolism and elsewhere but Comar et al. introduced it specifically for the strontium-calcium pair and did not quote any previous use of the term.

TABLE 13.5. Strontium-Calcium Discrimination Factors in the Rat

Diet	Milk	Milk and corn	Commercial
OR urine-diet			
OR blood-diet	4.3	3.4	5.2
DF urinary	.84	.84	.88
DF absorptive	.68	.66	.34
OR retained=	.57	.56	.30
(DF urinary) (DF absorptive)			

Source: Reset from Comar, Wasserman, and Nold 1956. Reprinted with permission of the Society for Experimental Biology and Medicine, New York, copyright 1956.

The discrimination in lactating animals has been worked out in many species, including the human. In the lactating goat (Wasserman, Lengemann, and Comar 1958), the DF absorptive averaged 0.24, the DF_{urinary} averaged 0.60 and the DF_{lactational-milk} averaged 0.61. Thus, the OR_{milk-diet} was about 0.09 (i.e., $0.24 \times 0.60 \times 0.61$), or an overall discrimination factor of about 11.1.

Discrimination factors for the lactating cow and human were found to be similar, i.e., average OR_{milk-diet} about 0.11 or an overall discrimination factor of about 9 in the cow and 0.10 and 10, respectively, in round numbers in the human. The results of these processes and the influence of diet in the lactating cow can be seen in the figures illustrated in table 13.6. Note that the percentage of the daily dose of ⁴⁵Ca appearing in milk is about ten times the percentage of ⁸⁹Sr, whether expressed in terms of daily dose per liter or per day, while the amount of calcium in feces and in urine is less than strontium, although only

TABLE 13.6. Levels of Ca⁴⁵ and Sr⁸⁹ in Milk and Excretions of the Lactating Cow at Steady State

Treatment	Cow No.	Milk		Milk		Feces (by excretion)		Feces (by difference)		Urine	
		Ca ⁴⁵	Sr ⁸⁹	Ca ⁴⁵	Sr ⁸⁹	Ca ⁴⁵	Sr ⁸⁹	Ca ⁴⁵	Sr ⁸⁹	Ca ⁴⁵	Sr ⁸⁹
		(% daily dose per liter)		(% daily dose per day)		(% daily dose per day)		(% daily dose per day)		(% daily dose per day)	
Low calcium	3	1.1	0.092	16.	1.4	68	82	67	94	0.64	1.4
	10	1.4	0.19	11.	1.4	45	76	71	92	0.38	1.3
	Mean	1.2	0.14	14.	1.4	56	79	69	93	0.51	1.4
Normal calcium	5	0.68	0.079	8.3	0.84	70	86	73	95	1.1	1.4
	8	0.97	0.080	12.	0.96	65	86	73	97	1.4	1.2
	Mean	0.82	0.080	10.	0.90	68	86	73	96	1.2	1.3
High calcium	4	0.47	0.035	6.	0.43	71	94	86	97	2.3	1.2
	6	0.33	0.047	2.4	0.34	86	99	94	97	1.1	1.1
	Mean	0.40	0.041	4.2	0.38	78	96	90	97	1.7	1.2
High strontium	7	0.61	0.065	5.2	0.56	92	100	81	95	3.1	2.4
	9	1.4	0.17	11.	1.4	58	84	77	95	2.3	1.5
	Mean	1.0	0.12	8.1	0.98	75	92	79	95	2.7	2.0

Source: Reset from Comar and Wasserman 1960. Reprinted with permission of the Society for Experimental Biology and Medicine, New York, copyright 1956.

slightly less. The excretion of strontium in urine is not greatly different from calcium, except on a low-calcium diet.^(a)

Note that the experiment was on animals in a steady state, i.e., no changes in dietary intake or in the metabolism of the organism were occurring (e.g., the animal was not growing, the diet was constant, etc.). We will return to this point in part 6 of this section.

Physiological processes showing little or no discrimination between strontium and calcium are: blood to skeleton^(b) (Comar and Wasserman 1960; Bauer, Carlsson, and Lindquist 1955); also excretion of the two elements from blood into the intestinal tract via the intestinal mucosa, the bile, and pancreatic juices (Greenberg and Troescher 1942) appears to be comparable.^(c) We have already seen that discrimination in the soil-root system for strontium-calcium is frequently considered to be negligible. A table of actual figures taken from experimental work at UCLA is shown as table 13.7.

TABLE 13.7. Strontium-Calcium Discrimination Factors for Plants Grown in Various Soils Under Different Conditions

Plant	Basis for* calculation	Number of soils studied	Extracting solution	Culture method	D.F. value
Barley	II	1	NH ₄ Ac(pH 7)	can (3.5 kg)	0.39-0.45
Buckwheat					0.43-0.49
Cowpeas					0.37-0.53
Barley	III	2	NH ₄ Ac(pH 7)	pot	0.90-1.07
Cabbage					0.85-1.07
Native Plants	II	1	0.1 N HCl	lake bed	~ 1
Corn					~ 1
Alfalfa	II		—	can (1 gal)	0.84-1.12
Wheat					1.01-1.23
Bean	I	3	NH ₄ Ac(pH 7)	pot (1.6 kg)	0.2-1.3
8 grass species	I	3	NH ₄ Ac(pH 9)	crock (1 gal)	0.8-1.5
8 legume species					0.8-1.3
Rice	II	—	—	pot	0.7-0.79
Wheat					0.61
Beans					0.76

*Basis for calculating the discrimination factor: I, stable Sr/stable Ca ratio; II, radio-Sr/stable Ca ratio; III, radio-Sr/radio-Ca ratio.

Source: Reset from Nishita, Romney, and Larson 1965. Reprinted with permission of Elsevier Science Publishers, Amsterdam, copyright 1965.

- (a) Note that these are not OR values and that the ratio in the diet is not given in the table. Thus, any DF values derived will not be in the same terms as those we have been using.
- (b) Comar, Wasserman, and Nold (1956) suggest that strontium in the blood may actually be preferentially deposited in bone, but the small amounts of radiostrontium in the blood made accurate measurements difficult.
- (c) There is some evidence that about twice as much radiostrontium as calcium is secreted into bile (unpublished observations in Comar's laboratory), but the total excretion of radiostrontium into the gastrointestinal tract is only about 20% greater than that of calcium.

These were all laboratory-type experiments or field experiments under controlled conditions. Obviously, there are many conditions under which the strontium-calcium discrimination in soil to plant is well below unity. These refer to the whole plant; DF values for different parts of plants can vary considerably. Thus, Auerbach and Crossley (1958) found in the corn experiment in White Oak Lake bed at Oak Ridge that the DF (strontium-calcium) could be 0.5 for the grain and 2.8 for the flower. There are many other examples of differences between parts of plants (see, for example, Nishita, Romney, and Larson 1965). These show that there can be discrimination within plants as well as between soil and plant. Similar differences between parts of plants have been found with the cesium-potassium and the rubidium-potassium pair.

In hazard evaluation, it is conservative to assume no discrimination at the soil-plant step. This, plus the considerable spread in experimentally obtained values, underlies the common practice. The research shows that this is not always true or that simple (see specific researches on plants).

Formulations for lactational discrimination and for placental discrimination are somewhat more complicated but utilize the same principles. These are shown as note 4 at the end of this chapter.

5. Mechanisms for Discrimination

The possible mechanisms underlying the phenomena of discrimination between strontium and calcium have been subjected to very active experimental investigation. The mechanisms uncovered undoubtedly apply to many other discrimination processes.

An early approach was on the basis of homeostatic control. In higher vertebrates, calcium content of blood and tissues is under fairly rigid control (i.e., homeostasis). As we will see in chapter 19, one of the severe limitations on the therapeutic removal of radionuclides deposited in bone is possible interference with calcium homeostasis, particularly the removal of excessive amounts of calcium. Strontium metabolism is not regulated around some normal concentration of stable strontium, i.e., there is no homeostasis for it. It is not surprising, therefore, that it behaves differently from calcium, but why should the difference always be in one direction?

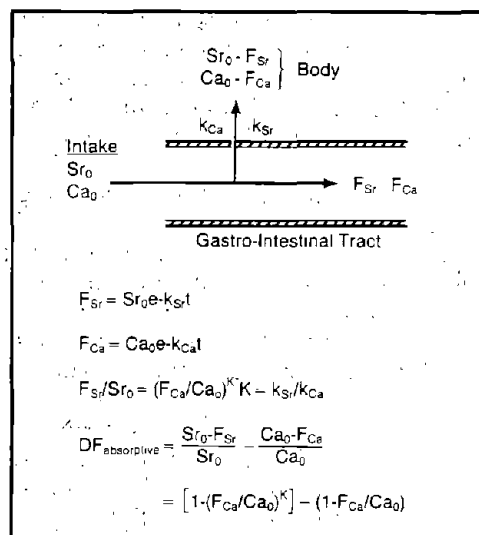
A second approach depends upon the relative rate constants for transfer across biological membranes. If calcium, for example, is absorbed from the gastrointestinal tract faster than strontium, there will in time be an enrichment of strontium in the remainder solution. The processes can be considered to have first order kinetics and can be modeled as in figure 13.15. The final solution from figure 13.15 can be written as:

$$DF_{\text{absorptive}} = \frac{1 - (F_{\text{Ca}}/Ca_0)K}{1 - F_{\text{Ca}}/Ca_0}$$

where K represents the comparative fractional rate constants for strontium and calcium (Comar 1967), F_{Ca} is calcium in feces, and Ca_0 is the stable calcium.

Marcus and Wasserman (1965) found that this equation held for gastrointestinal absorption in rats; and similarly Walser and Robinson (1963) found that it could apply to tubular reabsorption in the kidney of dogs and humans. The value of K was about 0.7 in these cases.

FIGURE 13.15. Expression of discrimination in terms of rate constants. The expressions F_{Sr} and F_{Ca} refer to amounts in feces, and are thus a rough measure of the amount not absorbed. K is the ratio of the rate constants K_{Sr} and K_{Ca} . (Redrawn from Comar, 1967; Reprinted with permission of Academic Press, New York, copyright 1967.)



The kinetic analysis needed to be fleshed out with more penetrating mechanistic investigations. This was carried out in several of the laboratories reviewed in sections I and II. Two of the approaches used will be considered here; first, the knowledge gained by research in which conditions were changed, and second, direct studies of physiological processes.

The first approach includes, but is not limited to, the effect of diet and age. It was found that the data shown in figure 13.10 could be explained by changes in the $DF_{absorptive}$ (DF_A). Harrison, Raymond, and Tretheway (1955) in the United Kingdom measured DF_A in infants as 1.06, i.e., essentially no discrimination. By contrast, work of Spencer et al. with adult humans found an average DF_A of 0.42. The $DF_{urinary}$ was about the same in both, viz., 0.79 in infants and 0.70 in adults. This work showed that the gastrointestinal tract of the infant lacks the mechanism operating in the adult. This may well relate to other known defects in the gastrointestinal tract absorptive mechanisms of infants.

The effects of dietary changes have pointed indirectly to mechanisms. For example, lactose fed to rats raises the DF_A value. It turned out that it did so by increasing calcium absorption (Marcus and Wasserman 1965).

As early as 1959, Schachter and Rosen (1959) demonstrated in isolated intestine that radiocalcium is actively transported, while strontium ions are not. Also, Wasserman, Kalfetz, and Comar (1961) used an everted rat duodenal sac preparation and showed that calcium could move against a concentration gradient in the absorption process, prima-facie evidence of an active transport process. Furthermore, the process seemed to depend on keeping intact the processes of oxidative phosphorylation (Taylor 1967). This was based on the effect of specific inhibitors of oxidative phosphorylation.

Comar and Wasserman (1960) mention seeing two phases of adaptation to decreases in dietary calcium as measured by calcium and strontium absorption. They speculate that one of these may represent the active transfer process, which appears to be easily saturated and cannot account for the whole of calcium transport under many circumstances.

Palmer and Thompson from Hanford (1961) used a somewhat improved technique by perfusing a segment of the rat intestine *in vivo*. This followed earlier methodology used by workers at Harvard (Dumont, Curran, and Solomon 1960) that had already shown that absorption of strontium followed kinetics of a passive diffusion process, while that of calcium showed evidence of an active transport process at higher concentrations of calcium in the intestine. While Palmer and Thompson claim that their work was not designed to elucidate mechanisms of absorption but only to measure discrimination during absorption, and it is true the data do just that, they show that discrimination does occur in the intestine. We view that as mechanism oriented.

Palmer and Thompson used ^{85}Sr and ^{45}Ca , the familiar double tracer of the time, and found that the percentage of ^{85}Sr absorbed was 0.3 that of calcium when no calcium was added to the perfusion fluid. As calcium concentration in the perfusion solution was increased, the amount of both ions absorbed decreased, but the ratio of ^{85}Sr to ^{45}Ca increased to about 0.6.

Still further into detail, Comar (1967) referred to work under way in the Cornell laboratories that indicates the following: strontium and calcium enter the intestinal mucosal cells at about the same rate, but calcium is moved out at a faster rate. This faster rate of transport may rest on the presence of a binding factor for calcium. This factor is considered to be a protein or associated with a protein.^(a)

What of the discrimination process in the kidney? The Walser and Robinson work was first developed to illuminate renal discrimination. They concluded that the value of K , the ratio of the rate constants k_{Sr} and k_{Ca} , is about 0.7. Comar followed this up (1967) in work evaluating the relation between $\text{OR}_{\text{urine-diet}}$ and urinary calcium concentration. Seemingly intuitively he concluded that the physical meaning of the ratio of rate constants $k_{\text{Sr}}/k_{\text{Ca}}$ represented the ratio of rate constants for tubular reabsorption of strontium as compared to calcium. Thus, the value of 0.7 (actually 0.5 to 0.7) would imply less reabsorption of strontium in the kidney tubule compared to calcium. The argument for the relationship is somewhat torturous, but erudite. The reader is referred to Comar's exposition for details.

Direct measurements of renal clearance and reabsorption were made in U.K. children (Arneil 1967) using samples of blood and urine and activation analysis techniques. The ratio strontium/calcium was higher in the urine than in the plasma in all but one case. Reabsorption of calcium in the renal tubules was calculated to be about 99%, while there was less reabsorption of strontium by about 3% to 5% and thus more strontium in the urine.

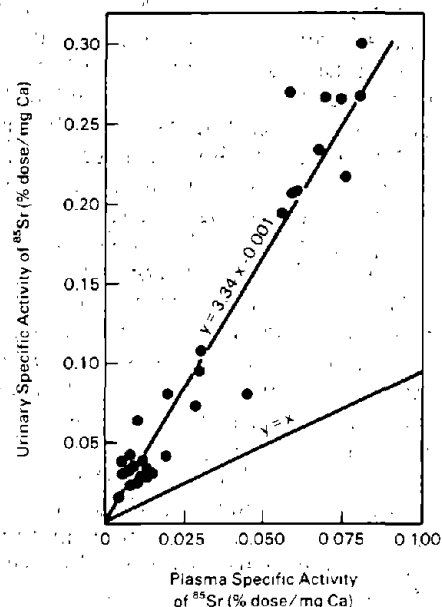
Della Rosa, Smith, and Stannard, at Rochester (1961), did a full study of renal clearance and tubular reabsorption of calcium and strontium in trained dogs. They found, using endogenous creatinine to determine glomerular filtration, that ^{85}Sr cleared from the plasma at an average rate of 0.91 ml/min, while ^{45}Ca cleared at a lower rate, about 0.17 ml/min. Tubular reabsorption of calcium was about 99%, i.e., almost complete, while that of strontium was lower, about 97%. These processes can account for the discrimination between strontium and

(a) This seems very simple in view of today's sophisticated work in membrane biophysics. Active calcium transport in membranes remains under intensive study. It is a pity that the powerful tools of current membrane work were not available when this work on discrimination factors was most active. The problems should be re-examined in a good membrane biophysics laboratory.

calcium in the kidney with the difference in reabsorption probably being the most important.^(a)

Work in the United Kingdom (Shimmins et al. 1967) concludes that a factor of 3.34 exists in the kidney in favor of strontium over calcium excretion. This research used the double-tracer method and human patients. They consider that the effect may reside in differences in protein binding, but they did no renal clearance studies. The discrimination value was obtained from the slope of a line relating urinary specific activity to plasma specific activity as shown in figure 13.16.

FIGURE 13.16. The discrimination against the re-absorption of ^{85}Sr by the renal tubules obtained from the measurement of simultaneous plasma and urine samples; correlation coefficient, $r = 0.92$. No discrimination would yield the line marked $y = x$. (Redrawn from Shimmins et al. 1967. Reprinted with permission of Academic Press, New York, copyright 1967.)



It should be obvious that any quantities resulting from research under a given set of conditions may or may not apply to others. Of special importance is the age of the subject, as we have already seen. There appear to be other changes that occur with time and may reside in changes in the chemical form(s) of the elements as presented for excretion. Thus, Thompson and Hackett (1967) reported a study in rats receiving a single intraperitoneal injection of ^{45}Ca - ^{85}Sr . They were able to measure the amounts of each circulating in the plasma and the amounts excreted per day in urine and feces over a fifty-day period. The amounts decreased with time as expected, with the decrease in body burden but not in unison. First, the amount in urine fell off to a larger extent than the amount in feces, and second, the change with time was much less for ^{45}Ca , only to about one-half the initial, than for ^{85}Sr , which fell to about one-sixth of the initial level. The result was, of course, an increase in the urinary-fecal ratio with

(a) The ultrafilterable fractions of ^{85}Sr and ^{45}Ca in plasma were about the same. A difference between 99% and 97% reabsorption may seem small until one realizes that this alone could account for a factor of three in the final excretion. The Rochester work included also manipulation of plasma calcium levels by parathyroidectomy or parathyroid extract, metabolic acidosis, etc. None of these changed the ratio of excreted strontium to calcium.

time and also changes in the strontium/calcium, so that the observed ratio also changed with time, as seen earlier in figures 13.10 and 13.11. The explanation seemed to reside in considerable change in intestinal clearance with time with very little change in renal clearance. The figures are shown in table 13.8.

TABLE 13.8. Clearance Data

	After 7 days deposition (Group II)	After 47 days deposition (Group I)
<i>Calcium-45</i>		
Circulating in plasma*	0.51 ± 0.11	0.084 ± 0.022
Excreted/day in urine*	1.1 ± 0.4	0.17 ± 0.07
Excreted/day in feces*	2.2 ± 0.4	0.74 ± 0.28
Renal clearance†	2.3 ± 0.9	2.2 ± 1.1
Intestinal clearance†	4.3 ± 1.1	9.1 ± 3.4
<i>Strontium-85</i>		
Circulating in plasma*	0.20 ± 0.04	0.018 ± 0.007
Excreted/day in urine*	3.2 ± 0.5	0.22 ± 0.05
Excreted/day in feces*	1.3 ± 0.4	0.49 ± 0.19
Renal clearance†	15 ± 3	13 ± 6
Intestinal clearance†	6.6 ± 1.2	30 ± 19

*Expressed as % of current body burden \pm s.d.

†Expressed as plasma volumes/day \pm s.d.

Source: Reset from Thompson and Hackett 1967. Reprinted with permission of Academic Press, Inc., New York, copyright 1967.

Note that renal clearance of ^{85}Sr was about six times the clearance of ^{45}Ca at both seven and forty-seven days, in line with the postulated mechanism for the discrimination described earlier.^(a) Note also that intestinal clearance of both elements was higher than the renal clearance, and that it rises with time for both, rather than remaining approximately constant. The intestinal clearance of strontium increased more with time than that of calcium so that the ratio of intestinal clearance rates (strontium/calcium) went from about 1.5 at seven days to 3:2 at forty-seven days. This implies possible changes in the form of calcium and strontium in the blood to one more readily excreted via the intestine or less readily reabsorbed and that the process occurs to a greater extent with strontium. Such changes in physicochemical state of deposited radionuclides with time after deposition in blood and tissues have been noted on several occasions in this book. Note, for example, the work with polonium in chapter 4, the behavior long-term of the fission products and actinides in chapter 8, and some of the dilemmas of lung retention seen in chapter 9. For the case at hand, the authors propose as "not inconceivable" that calcium and strontium released from stable binding sites in bone or other tissues may exist in different chemical forms than when they entered the blood stream. From what we have learned in

(a) This was overall renal clearance, not the tubular-reabsorption figures.

this book, this author would propose that such a change is almost inevitable, particularly since, as the concentration decreases, the portion that is in radiocolloidal form may decrease considerably.

Another possibility involves the relative roles of the several compartments into which radionuclides are deposited from the blood stream.

There are many radionuclides (see earlier chapters) for which the ratio of urinary to fecal excretion changes with time. Probably most of these involve changes in the state of the nuclide as presented for excretion.

What information do we have on the relative retention of strontium versus calcium in bone? Here we must go back to the Metallurgical Laboratory work at Chicago (chapter 6). Norris and Kisielski (1948) reported that strontium is retained in skeleton to a lesser extent than is calcium, a "discrimination" of sorts, again in the direction of protecting the body from the more toxic element. Bauer, Carlsson, and Lindquist (1955), working in Sweden, were among the many who approached the general problem of metabolism of the two elements in bone and decided that the explanation for the lower retention of strontium resided in the discrimination processes we have already discussed, not in processes in bone itself. The skeleton seems unable to distinguish between the two elements, at least, grossly.^(a)

We thus have evidence that the three most important discrimination processes involve active biological processes. So also does the discrimination in the placenta. Can we conclude that Mother Nature developed these because she knew that humans would do something foolish like contaminating their environment with fallout? We cannot dismiss such ideas out of hand, but we can be less anthropocentric. In the case at hand, we need only remember that calcium is a key element in higher animals and is regulated zealously. Strontium neither occurs in organisms naturally in significant quantities, nor is it a key element. There are no homeostatic regulatory mechanisms for it. Hence, a difference in metabolism between the two is not surprising.

Many other mechanisms may allow discrimination between pairs of elements, e.g., relative ionic radii, relative charge, degree of hydration, relative half-life, any of which could yield a pseudodiscrimination. Also, some elements reside primarily within cells, others are primarily extracellular. Although these processes play a role in the behavior of radionuclides in the biosphere, they seem unlikely to be of controlling importance for the fallout nuclides in higher organisms.

The obverse of discrimination, viz., concentration, is a more universal phenomenon in the uptake of radionuclides in biological materials. As we have seen, these processes and the associated "concentration factors" are resident largely, but not only, in the way and extent to which the element participates in the metabolism of cells and tissues.

6. Practical Overtones

Much of the research described above was motivated by the desire to understand physiological and biochemical mechanisms. The basic concepts were formulated, however, as much to aid in the evaluation of hazard as to delineate mechanisms. We did need to know the transfer factors to the diet and from diet to humans (Wasserman et al. 1965) and have seen already that the postulates for the systems were met sufficiently well to satisfy their sponsors and all but the

(a) The extensive work on bone biochemistry fine tunes this statement a bit.

most concerned critics. There have been a few opportunities to test the results obtained through calculations based on data from environmental contamination and field research. We will consider some of these briefly in this section.

We can start with the fact that the OR for $^{90}\text{Sr}/\text{Ca}$ in desert animals was reasonably comparable to that in laboratory animals raised on commercial diets. Thus, observed ratios for Nevada desert animals were 0.2 for jack rabbits, 0.22 for cottontail rabbits, and 0.16 for kangaroo rats (Alexander, Nusbaum, and MacDonald 1956), compared to 0.35 in laboratory mice, 0.27 in laboratory rats, and 0.22 in laboratory guinea pigs (Comar, Wasserman, and Nold 1956). This is not perfect agreement, obviously. The OR values in the laboratory seemed to be fairly consistently higher than in wild animals of related species. Thus, we find that Cohn, Robertson, and Conard (1960), who examined the same data, suggested that the appropriate value for $\text{OR}_{\text{bone-diet}}$ would be 0.16 for the wild kangaroo rats in the Nevada desert compared to the commonly used blanket value of the OR of 0.25 for the experimental situation.

Research and field work in the Marshall Islands provided an excellent opportunity to test the ratio system and its parameters. A key discussion was presented by Cohn, Robertson, and Conard from Brookhaven (1960) at the Minneapolis symposium. As related in chapter 12, this group measured fission product uptake, distribution, and concentration in soil, plants, diet, aquatic forms, animals, and the Marshallese. To make an estimate of body burden of strontium from environmental contamination, they first used data on the $^{90}\text{Sr}/\text{Ca}$ ratios measured in rats collected on Rongelap. Since the ratio in the diet varied considerably in different foods, they had to use the ratio in soil as a surrogate for that in average diet. They extrapolated the environmental data to an expected equilibrium value and compared this to actual measurements in the animals. The extrapolation value, 924 pCi $^{90}\text{Sr}/\text{g Ca}$, was about twice the values measured by radiochemical analysis of animals that had lived on the island for two years following contamination, viz., 470 to 545 pCi $^{90}\text{Sr}/\text{g Ca}$. Did this mean the animals were not yet in equilibrium with the diet? Probably not, since animals analyzed at four years after contamination had closely similar ratios, viz., 443 ± 181 pCi $^{90}\text{Sr}/\text{g Ca}$. Therefore, other factors must have underlain the difference. The authors could not pinpoint any single factor but were inclined to attribute the problem to difficulties in determining the OR from soil to plants.

The measurements on the Marshallese were even less satisfactory. While estimates of body burden made by calculation from radiochemical analysis of urine agreed reasonably well with direct measurements made with the whole-body counter, the calculations from the $^{90}\text{Sr}/\text{Ca}$ ratios in diet varied widely. Examination of the input data from the diet provided an explanation. The diet of the Marshallese was far from constant, partly because of varying proportions of imported food such as "C" rations, partly because of varying input and composition of indigenous foods, and partly because of the discontinuous nature of their residence on Rongelap Island. Cohn et al. reviewed the various estimates of average dietary intake and decided that neither the Marshallese nor the animals had reached equilibrium (or a steady state), and reliable estimates from the environment could not be expected.

Much the same situation occurred in the determination of ^{137}Cs body burden in the Pacific islands, with the same factors responsible. With cerium, there is the added factor that its half-life is relatively short, and the calculation of steady-state value must be adjusted to consider radioactivity equilibrium as well as dietary input versus output.

The laboratory research indicated, while the field studies confirmed, that predictions of body or organ burden (e.g., skeleton) were not reliable if the system was not in equilibrium (or more precisely in a steady state). The environmental situation in the Marshall Islands was probably one of the least likely choices to meet that criterion. Was it better in other situations?

The 1966 international symposium on strontium metabolism held in Scotland in May 1966 came at a time when these questions were being considered very actively. Enough data had accumulated to provide reasonable chances to test the models based on experimental research. There were several summary papers there that we can utilize to approach the above question.

Joseph Rivera from the AEC Health and Safety Laboratory (HASL) played an important role, along with John Harley and others, in gathering the mountains of data on diets in New York City, Chicago, and San Francisco (chapter 12). Rivera (1967) compared the $^{90}\text{Sr}/\text{Ca}$ ratios to be expected from the diets to observations of ^{90}Sr vertebrae from accident victims in the same cities. He used three models: (1) one that assumed no change with age in replacement rate of skeletal calcium (f) or the bone-diet DF for strontium-calcium (which he designated as K); (2) one that assumed $f = 0.50$ and $K = 0.35$ during the first year of life and remained constant at $f = 0.035$ and $K = 0.25$ from that time on; and (3) a third model that assumed f and K varied with age from year one to year twenty over a range from 0.50 to 0.24 for f , and 0.35 to 0.13 for K , respectively. The predicted versus observed $^{90}\text{Sr}/\text{Ca}$ ratios for the period 1961 to 1965 agreed best for New York, poorest for San Francisco. If New York and San Francisco were combined, the second model worked best. However, the differences are difficult to take seriously. Choosing values of $f = 0.50$ and $K = 0.35$ clearly produced the best agreement between predicted and observed $^{90}\text{Sr}/\text{Ca}$ ratios during the first three to four years of life. Rivera was pleased in general with the figures obtained and concluded that ^{90}Sr levels in diet could predict average bone levels in children to about $\pm 25\%$ using the ratio method.

At the same symposium, Lenihan, from Glasgow, correlated ^{90}Sr levels in fetal bone with the concentration in milk (Lenihan 1967). The amount in bone after birth could be forecast from a knowledge of the concentration in milk for periods up to eighteen months. Both diet and bone figures were reported as $\text{pCi } ^{90}\text{Sr}/\text{g Ca}$. Bone and milk levels were rising with time over the period because of the gradual increase of ^{90}Sr in the environment. These, plus the comparison of observed to predicted levels, are shown in table 13.9A and B.

The agreement is reasonably close between observed and calculated values. Evidently, the rise in ^{90}Sr levels was gradual enough so that the fetal bone and maternal diet were in a quasi-steady state. This might not have held for adult bone, which accretes strontium more slowly than fetal bone.

An interesting exposition of some of the differences in environmental parameters between the USSR and the United States is given by Knizhnikov and Marei (1967). They point out that the daily intake of ^{90}Sr in the diet in the years 1963-1964 was considerably greater in the Soviet Union than in the United States; yet, the level of ^{90}Sr in human bone was about the same in various age groups in the two countries. They suggest two factors that might be responsible: (1) bread and grain represent the major source of dietary ^{90}Sr (and calcium) in the Soviet Union, whereas milk and dairy products play that role in the United States; and (2) fallout strontium deposited on growing crops is less soluble and less effectively absorbed in the human than the more soluble forms in dairy products.

TABLE 13.9A. Strontium-90 in Milk and Bone

Year		⁹⁰ Sr (pCi/g Ca)	
		Milk*	Bone† (0-14 day age group)
1960	January-June	9.8	
	July-December	6.8	
1961	January-June	6.9	0.79
	July-December	8.0	1.04
1962	January-June	10.4	0.85
	July-December	23.2	1.41
1963	January-June	19.1	1.65
	July-December	47.6	3.37
1964	January-June	38.8	3.42
	July-December	34.6	4.00
1965	January-June	29.0	3.24
	July-December	22.3	

*Average for Scotland.

†Average for Glasgow region.

TABLE 13.9B. Strontium-90 in Bone: Comparison of Predicted and Observed Levels (Glasgow Region)

Year		⁹⁰ Sr (pCi/g Ca)	
		observed	calculated
1961	January-June	0.79	0.80
	July-December	1.04	0.73
1962	January-June	0.85	0.85
	July-December	1.41	1.47
1963	January-June	1.65	1.64
	July-December	3.37	3.21
1964	January-June	3.42	3.27
	July-December	4.00	4.06
1965	January-June	3.24	3.40

Source: Reset from Lenihan 1967. Reprinted with permission of Academic Press, Inc., New York, copyright 1967.

The OR between bone from stillborns and maternal diet in the USSR work was about 0.053 over the period 1964-1965, considerably lower than that employed in any of the three models for U.S. diets by Rivera. That for the maternal skeleton to the natural diet was about 0.20. Their data showed a decrease in the discrimination coefficient (factor) for ⁹⁰Sr as a function of age in children, but it was very low for both stable strontium and ⁹⁰Sr in the fetus.

In this work, it was found also that another environmental factor could play a role, fluoride in drinking water. Some areas of the USSR, like some in the United

States have quite high natural fluoride contents in their drinking water. Knizhnikov and Marei (1967) found that the ^{90}Sr contents of human bones were lower in towns having such drinking water.

This work emphasized again the point made earlier in chapter 12 that predicted strontium bone burden will be different for diets with large components of milk and dairy products, on the one hand, versus grains and cereals on the other. If due cognizance is taken, the predictions are about equally satisfactory for Western and Eastern (Far-Eastern) diets.

Liniecki, from the Institute of Occupational Medicine at Lodz, Poland (Liniecki 1967), calculated ^{90}Sr concentrations in bones of adults by applying a power function for strontium retention. Again, all data were reported as $\text{pCi } ^{90}\text{Sr/g Ca}$ for both the diet and bone. Good agreement was obtained between predictions from diet and direct measurements in bone for New York City, Poland, and Great Britain.

Finally, we turn to a strictly research approach, i.e., not based on ambient environmental parameters, but pertinent nevertheless. This is a study by Rundo (1967) who was then at the U.K. Atomic Energy Research Establishment and is now at ANL in the United States. Healthy men were placed on a constant diet for twenty-one to thirty-two days that contained milk and tracer doses of the short-lived ^{85}Sr . Retention curves were best fitted by three exponential components rather than a power function.^(a) Experimental observations (whole-body counting) were in respectable agreement with the skeletal content predicted by the equations.^(b)

To a degree, all of the environmental and some of the experimental data considered above for strontium/calcium ratios have been incomplete in that they used a "shortcut." As Comar (1967) pointed out, the theoretically correct method would utilize either the ratio of the two stable elements or a double tracer such as the ^{85}Sr - ^{45}Ca . Comar addresses the question of the extent of error introduced by using the single tracer method, i.e., $^{90}\text{Sr}/\text{Ca}$. His analysis is based on pool sizes and timing. The rapidly exchangeable body pool for strontium and calcium is considered to be small (about 5 g of calcium and 1.7 mg strontium in man), but the urinary strontium and cesium come from it. The slowly exchangeable pool, which is bone, is larger (e.g., 1,000 g calcium and 345 mg strontium). Using data for ingested stable strontium in man, Comar concludes that, at ten days after a change in intake, the measurements would be in error by about 10%. Also, if the dietary intake has been more or less constant over a moderately long period, the "shortcut" method gives a good approximation. However, if dietary $^{90}\text{Sr}/\text{Ca}$ levels are changing rapidly, the calculated skeletal or body burdens will be in error and require several days to reach a new equilibrium or steady state after each such change.

Comar concludes that, in growing children or in the presence of changing dietary patterns, the double tracer or full-balance study may be required. This is, of course, not practical in most environmental situations. However, the question was left open as to how much the pool characteristics change under these circumstances. If they do not change very much, the "shortcut" may not be too misleading.

It was much the same story with cesium. The apparent lack of reliable correlation between it and potassium led to less emphasis on how well the body

(a) See chapters 7 and 8 for discussions of the pros and cons of these representations.

(b) The data were not reported as strontium/calcium ratios.

content of it could be predicted from parameters such as the cesium/potassium ratio. Langham and Anderson (1959, p. 42) engaged in the following calculation for ^{137}Cs from fallout: "If 1 mc/mile² gives 30 pc/g available soil potassium and the average surface deposition (December 1957) in the north temperate population belt was 36 mc/mile², the average ^{137}Cs level in people (assuming entry through the ecological cycle) would be $30 \times 0.03 \times 36 = 32$ pc/g K. People in the vicinity of 40°N-45°N (Washington State, the Dakotas, Minnesota, and Wisconsin) would average about 64 pc/g K."^(a)

Measured values of cesium in people during the fall of 1957 were surprisingly close to these calculated figures. However, Langham and Anderson considered it might be entirely coincidental and "could result from direct fallout on vegetation fortuitously making up for non-equilibrium of Cs^{137} with exchangeable soil potassium" (Langham and Anderson 1959, p. 42).

These authors, and many others, believed that direct deposition on vegetation played a central role in the entrance of cesium into the biosphere because of its high fixation in soil, its slow leaching rate, and the fact that the $^{137}\text{Cs}/\text{K}$ ratio in people and milk did not seem to be rising in relation to integrated fallout. They estimated that equilibrium levels in people who received the radionuclide by the soil route would not be reached in less than one hundred years because of the slow mobilization of cesium from soil. Since this mechanism would also predict a slow decline in cesium levels when testing ceased, and it was actually quite rapid, their skepticism about the agreement, noted above, may have been justified.

Much more on the behavior of cesium can be seen in the many reviews cited, including the one by Wasserman et al. (1965) in the Fowler book that considers most of the important radionuclides in fallout.

Work similar to that we have been quoting continued for many years but at a declining pace. As the fallout problems lessened, so did the pressure to test in the practical arena the ideas generated by the research. Nevertheless, the practice of reporting strontium and cesium as ratios to calcium and potassium, respectively, continued for a long time. This attests to the overall success of the ideas generated in the research in aiding evaluation of contamination of the environment and humans.

Perhaps the best evidence for this is seen in the 1977 United Nations report (UNSCEAR 1977). While some of the input figures are direct, i.e., not ratios, we find tables for strontium in milk given as the $^{90}\text{Sr}/\text{Ca}$ quotient, pCi/g Ca. The same is true for levels in bone in many countries and as a function of age.

By contrast, in the UNSCEAR documents, the levels of cesium are given sometimes as picocuries per liter of milk or as daily intake in picocuries and in other sections of the report as the $^{137}\text{Cs}/\text{K}$ quotient. The former are in tables where strontium and cesium are reported together. The latter appear in the section of the report on cesium where not only the amounts in diet but the transfer factors are given as ratios.^(b)

By the time of the 1982 UNSCEAR report, the quotient had disappeared completely and had been replaced by the linear parameter, Bq kg⁻¹ (UNSCEAR 1982). Naturally, there is no comment in the 1977 version as to why the quotient

(a) The 0.03 in the calculation comes from the OR for cesium calculated in figure 13.14.

The difference between the more northerly latitudes and the average was due to the more intense testing in this band, particularly the tests in Siberia.

(b) They called them, probably more properly, "quotients" rather than "ratios."

was considered worth keeping in use for so long, or why it is used in some contexts and not in others. Nor are there any remarks on its disappearance in the 1982 version. It is probably no longer needed. It may even be confusing in the context of environmental contamination around nuclear reactors, since here the chances of reaching equilibrium or a steady state are (happily) small. Also, the area involved is relatively small so that anything approaching uniform contamination of the diet or the environment is also unlikely. However, this is conjecture on the author's part and not based on any explanation given by the UN committee, since there was none.

The above discourse presents a few of the pitfalls as well as the successes in applying the ideas developed in the laboratory research to environmental contamination; i.e., the practical overtones. It is clear that the worst pitfalls are lack of equilibrium in the soil or diet and lack of a steady-state condition between the environment and the ultimate recipient. A glance at further work as seen, for example, in the selected publication list from Cornell (note 3) shows that research bearing on mechanisms thrived long after the major scare generated by fallout from weapons tests had subsided.

B. Aquatic Biology

There is ample general documentation in earlier chapters for the organizations, programs, and findings concerning the behavior and potential effects of radionuclides in fallout on aquatic organisms. No large experimental programs were designed specifically around the fallout problems produced in aquatic systems. The large observational programs already described (chapters 11 and 12) took up most of the time and talent. Nevertheless, enough strictly experimental work was done in the aggregate to warrant a short discussion separate from the large environmental and ecological enterprises.

Some of the effort concerned biokinetic behavior of radionuclides, and some concerned effects on aquatic biota. The former is primarily an extension of the vast observational studies already quoted. Since the results brought no real surprises, we will supply primarily samples with emphasis on earlier work. The work on effects extended the work with external radiation sources, alluded to earlier, to radionuclides in water. It will be described in compact form, partly because suitable reviews are available and partly because the bulk of the work was done in other parts of the world and must receive a lower priority in this review.

1. Uptake, Distribution, and Retention Under Laboratory Conditions

An early and useful insight into biokinetics in aqueous systems is contained in the report prepared by the Committee on Effects of Atomic Radiation on Oceanography and Fisheries of the U.S. National Academy of Sciences (NAS-NRC 1957) discussed in part in chapter 12. A full chapter therein is devoted to a summary of laboratory experiments on the uptake, accumulation, and loss of radioactivity from marine organisms (Boroughs, Chipman, and Rice 1957). There is also a careful analysis of the factors of importance to either laboratory or field research in chapter 7 (Krumholz, Goldberg, and Boroughs 1957).

The work shows that important factors governing the processes of concern are:

1. chemical composition of the organisms
2. concentration of the radionuclide

3. effect of the presence of one element on the uptake of another^(a)
4. specificity in organisms and tissues, based mostly on metabolic processes
5. ionic and osmotic conditions
6. stage in the reproductive cycle
7. presence or absence of molting
8. age and stage of growth
9. temperature
10. light
11. presence or absence of radiation effects.

Nearly all of the laboratory experiments described by Boroughs and colleagues took place at either the Fishery Radiobiological Laboratory of the U.S. Fish and Wildlife Service in Beaufort, North Carolina,^(b) where Rice and Chipman worked, or at the Hawaii Marine Laboratory of the University of Hawaii, where Boroughs worked. The experiments were classified according to the trophic level to which the organisms belonged.

Consider first the lowest trophic level, viz., plankton, etc. In twelve species of algae, the percentage of activity from strontium compared to yttrium, taken up from a culture medium with these in secular equilibrium, ranged from 100% strontium and 0% yttrium to 2.3% strontium and 97.7% yttrium in different species! There were also differences in the concentration factors relative to sea water among the twelve species.

By contrast, the uptake of cesium by nine species of marine algae was much more nearly uniform. Concentration factors ranged only from 1.2 to 3.1. No attempt is made to explain these differences, nor could such results have been predicted.

Considerable effort was devoted to the effect of concentration of the stable element in the medium on the percentage uptake of the radioelement. Most of the work concerned radioisotopes that could be presumed to be in ionic form in sea water, with the exception of ^{106}Ru , which forms colloids and particles in sea water.

At the second trophic level, work was done, for example, with larvae of the brine shrimp, *Artemia*; other shrimp; the blue crab; oysters; the bay scallop. All of these accumulated strontium rapidly from sea water, while cesium uptake was slower. The latter did not reach equilibrium for at least eighteen days, while the strontium uptake reached saturation in about eight days (see figures 4 and 5 in Boroughs, Chipman, and Rice 1957). The tissue distributions were also measured. The results were as expected from the experimental work with animals and the environmental studies on aquatic forms.

Fishes represented the highest trophic level. A considerable variety was studied to encompass the range between fast-swimming pelagic fish, such as dolphin, yellowfin, and skipjack, and ones like the sluggish bottom feeder, *Tilapia*. In some cases, the radionuclide was given to the fish orally in gelatin capsules to provide greater certainty regarding the dose. The sluggish fish with slow metabolic rates accumulated strontium considerably more slowly, and retention was also longer. It was clear that none of these fish took up more than a portion of the strontium and that discrimination could occur in these as in terrestrial

(a) A generalized version of the preceding discussion on the metabolism of pairs of elements.

(b) Later named Atlantic Estuarine Laboratory of the National Marine Fisheries Service.

animals and other organisms. Detailed analyses of the tissues revealed nothing unexpected.

It was clear that behavior of the radionuclides among species was much more uniform at this higher trophic level than in the algae. The chief differences at the highest trophic level resided in rates of movement tied to the level of metabolic activity.

Effective half-lives for several isotopes in several species of fish ranged from 6 to 841 days (see review by Rice and Baptist 1974). This is much less than the range of concentration factors. The considerable variability of these factors for several types of marine organisms can be seen in table 13.10. Note the large difference among ionic species for even noncalcareous algae.

TABLE 13.10. Approximate Concentration Factors of Different Elements in Members of the Marine Biosphere. The concentration factors are based on live weight.

Element	Form in sea water	Concentration in sea water (micrograms/l)	Algae (non-calcareous)	Concentration factors			
				Invertebrates		Vertebrates	
				Soft	Skeletal	Soft	Skeletal
Na	Ionic	10 ⁷	1	0.5	0	0.07	1
K	Ionic	380,000	25	10	0	5	20
Cs	Ionic	0.5	1	10		10	
Ca	Ionic	400,000	10	10	1,000	1	200
Sr	Ionic	7,000	20	10	1,000	1	50
Zn	Ionic	10	100	5,000	1,000	1,000	30,000
Cu	Ionic	3	100	5,000	5,000	1,000	1,000
Fe	Particulate	10	20,000	10,000	100,000	1,000	5,000
Ni*	Ionic	2	500	200	200	100	0
Mo	Ionic-Particulate	10	10	100		20	
V	?	2	1,000	100		20	
Ti	?	1	1,000	1,000		40	
Cr	?	0.05	300				
P	Ionic	70	10,000	10,000	10,000	40,000	2,000,000
S	Ionic	900,000	10	5	1	2	
I	Ionic	50	10,000	100	50	10	

*Values from Laevastu and Thompson (1956)

Source: Reset from NAS-NRC 1957, chapter by Krumholz, Goldberg, and Burroughs, p. 74.

Obviously, these so-called concentration factors could obtain much of their variability from differences in the basic amounts of the different elements in the surrounding sea water. They could be quite different in some cases if the base line were fresh water. Nevertheless, this possibility does not account entirely for the tremendous range of values for different elements. Some of it could have been predicted from metabolic behavior, but not all.

Concentration factors for freshwater organisms determined in the relatively early environmental work on the Columbia River and White Oak Lake also show a wide range among the elements and among organisms (Krumholz and Foster 1957). More limited laboratory work on the goldfish and the guppy showed concentration factors ranging only from thirty for sodium to one

thousand for calcium; this probably indicates only the scarcity of experimental data at the time the academy's report was written.^(a)

In view of the relative constancy of the mineral content of sea water and the chances for large swings in the concentration of many elements in freshwater, the chances, given sufficient data, are considered good that concentration factors in marine organisms would be more constant than those in freshwater organisms (Polikarpov 1967). Indeed, Polikarpov takes the view that work with aquatic systems should lead to the establishment of principles and "regularities" in radioecology more readily than work with terrestrial organisms. The laboratory data did not provide much support for this hypothesis, but there may not have been enough data at the time.

At the Stockholm symposium on radioecological concentration processes held in 1966 and published in 1967 (Åberg and Hungate 1967),^(b) there was a collection of reports pertinent to our subject. The Polikarpov review cited above leads off the collection. In addition, the volume contains a sophisticated kinetic analysis of isotope exchanges by marine organisms by Polikarpov et al. (1967).^(c)

Nelson, from Oak Ridge (Nelson 1967), introduced the idea that ^{90}Sr -uptake by fish could be predicted on the basis of specific activities and half-lives rather than on the strontium/calcium ratio discussed in the previous section. He devised a fish-holding assembly that allowed the equivalent of whole-body counts and also measured tissue contents. He found that for predictive purposes the results of the specific activity approach and the ^{90}Sr -Ca ratio were about equal, but that was because the exposure concentrations were more or less constant. He held that the specific activity approach would be more reliable for prediction when the input conditions regarding either calcium or strontium were not constant. Incidentally, the biological half-life of strontium in white crappie flesh was only twelve to forty-eight minutes. Thus, the flesh would be very responsive to changes in environmental ^{90}Sr concentrations.

Workers from Chalk River reported experiments with goldfish on radiostrontium accumulation from food as compared to water and the effects of the alkaline earth content of food (both natural and synthetic) on the retention of ^{90}Sr . There was not a simple answer to the question whether fish would generally accumulate more ^{90}Sr from food or water (Ophel and Judd 1967).

Townesley (1967), from the University of Hawaii, measured ^{90}Sr and ^{89}Sr and concluded that the specific activity in the surrounding medium could be the controlling factor on their absorption by fish.

Häsänen et al., from Helsinki, built a "whole-body counter" for live fish and studied the biological half-time of ^{137}Cs in three species (perch, roach, and rainbow trout). The biological half-times increased with increasing age and differed among the species (Häsänen, Kolehmainen, and Miettinen 1967).

(a) The work of Prosser et al. (1945) and Prosser, Hagen, and Grundhauser (1947) on goldfish done at Chicago under the auspices of the Metallurgical Laboratory was quoted prominently. They used sodium, strontium, and barium-lanthanum. Again, we must salute the vision of the early workers as discussed in chapter 11. It is rumored that they received a bit of twitting for fooling around with goldfish, especially when fission products were scarce!

(b) The bibliography of the papers cited at this symposium can provide a useful overview of what was going on at the time.

(c) The data were largely from natural environments, but the analysis was a research contribution in itself.

Van der Borcht and Van Puymbroeck (1967), from Mol, Belgium, produced evidence for active transport of alkaline earth ions in freshwater gastropods. There were also experiments with chromium in crabs, radioiron in marine diatoms, ruthenium in mussels, zinc in crabs and oysters, etc., which produced results like those we saw in environmental work.

Additional work can be characterized by even more selective samples. The study of ion scavenging by the eastern clam and quahog by Andrews and Warren (1969), cited briefly in an earlier section, provides an excellent example of work that can be done handily in a laboratory aquarium. The initial problem was that the animals seemed to fix greater quantities of various radionuclides than they retained. Using ^{131}I , ^{85}Sr , and ^{59}Fe , Andrews and Warren showed that the difference, as expected, resided in the large amount taken into the organism and incorporated with considerable concentration en route into the feces. Thus, both animals functioned to remove ambient concentrations from solution or suspension in the water and to transfer them to deposits on the laboratory equivalent of the ocean floor. There were slow and fast components in the rate at which the organisms depleted the sea water, and they differed. The slow component was more marked (i.e., slower) in the quahog for ^{59}Fe and ^{131}I , while for ^{85}Sr it was the clam that was much slower. The comparison of iodine and strontium is shown in figure 13.17A and B.

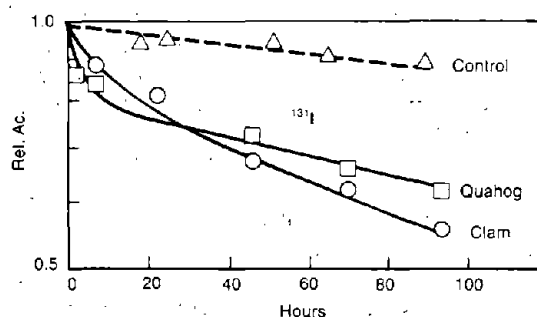
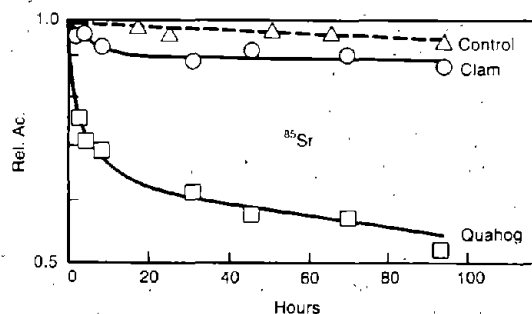


FIGURE 13.17A. Depletion curves for relative activities (Rel. Act.) of ^{131}I from sea water by bivalves. (Redrawn from Andrews and Warren 1969. Reprinted with permission of Pergamon Press, Elmsford, New York, copyright 1969.)

FIGURE 13.17B. Depletion curves for relative activities (Rel. Act.) of ^{85}Sr from sea water by bivalves. (Redrawn from Andrews and Warren 1969. Reprinted with permission of Pergamon Press, Elmsford, New York, copyright 1969.)



Again, and despite Polikarpov's contention that the aquatic environment should be relatively uniform regarding the behavior of radionuclides in organisms, we see unexpected differences between elements and between species, even as closely related as the clam and quahog.

Slightly later, we find mixed in with the observational work reported at the Third National Symposium on Radioecology held at Oak Ridge in 1971

experimental work on such questions as the effect of temperature on retention of radiocesium by rainbow trout done by workers at Colorado State (Gallegos and Whicker 1971), the uptake of phosphorus by rooted aquatic plants (Schults and Malueg 1971), the relative accumulation of soluble and particulate radionuclides by estuarine fish (Hoss and Baptist 1971), the biological half-lives for zinc and mercury in the Pacific oyster (Seymour and Nelson 1971), and the effect of calcium concentration on accumulation of ^{45}Ca by developing Coho salmon eggs and fry (Olson 1971).

The work with temperature in trout was built around the question of how the water temperature and the weight of the fish, which depended in turn on the availability and type of food in natural habitats, might influence the concentration of fallout radionuclides in the fish. Radiocesium was chosen as the test nuclide since primary interest centered on the soft tissues that might become food for humans. There was a clear relation between both temperature and weight, as a "weighted average weight/temperature interaction term," for radiocesium retention. The results implied that both maximum uptake and maximum retention would be achieved at water temperatures that were optimal for food production and consumption and thus growth of the fish—not surprising.

The work with rooted aquatic plants came from the Pacific Northwest Water Laboratory in Corvallis, Oregon, and was only indirectly a result of fallout problems. The plants used were of the type that have developed into real nuisances in many small bodies of water and waterways. The purpose was an evaluation of the cycling of radiophosphorus between sediment and the water medium, a variation of the problem we have encountered in other connections regarding "food" (in this case material absorbed through the roots embedded in the sediment) compared to direct absorption from the surrounding medium. A double tracer, ^{32}P versus ^{33}P , allowed separation of the pathways. There was higher uptake by the foliage immersed in the surrounding water than via the roots immersed in the bottom sediments, and very little of the latter was transferred down to the root medium. Thus, the source of nutrient could be earmarked as primarily water.^(a)

The work on estuarine fish (Hoss and Baptist 1971) came from the National Marine Fisheries Service at Beaufort, North Carolina. These fish were a natural candidate for laboratory study since conditions in estuarine waters can change rapidly. Hoss and Baptist looked at ^{65}Zn and ^{144}Ce , presumably in ionic form and ^{51}Cr in particulate form. The typical estuarine fish absorbed little of the radionuclide in particulate form except by surface adsorption; also, the presence of sediment reduced the uptake of ^{65}Zn and ^{51}Cr because of their adsorption on the sediment particles. The results suggest that, in these estuarine environments, swallowed water is a more effective pathway than ingested food, but this generalization can be modified by changes of conditions.

The biological half-life of ^{65}Zn and of mercury in the oyster (Seymour and Nelson 1971) was determined in a laboratory aquarium at the University of Washington, College of Fisheries. Average biological half-life was different in different seasons by a factor of over two. The calcium study that also came from the University of Washington (Olson 1971) found that the radioisotope accumulated in inverse proportion to the amount of stable calcium present.

(a) In nature, the bottom sediments may build up radioisotopes, but we are talking here of normal plant nutrition in an aquatic milieu.

Of some interest to those accustomed to the multiexponential retention equations seen in most animal experiments and described also for some aquatic systems is work by Cutshall (1974) from the School of Oceanography at Oregon State University, which considered uptake and loss of ^{65}Zn by Pacific oysters. Both processes were well described by a single first-order equation, which implies "single compartment" isotope substitution kinetics. The constants estimated from either intake or loss were roughly comparable. Would that the systems were always as simple as this one appears to be.

Each laboratory with major field programs had occasion to check out specific points in an aquarium or a pool. It started at Hanford, as described in chapter 11, and grew into most of the other laboratories. Most of the generalizations made earlier concerning aquatic ecosystems were confirmed by the laboratory investigations and made more quantitative.

The fact that radionuclide-organism interactions are much different in sea water than in fresh water was amply confirmed. Perhaps the largest surprise was the persistence of very individual kinds of behavior among organisms and among radionuclides. Going to the laboratory did not, as might have been expected, greatly reduce such differences. They could not, therefore, be attributed to "unknown factors" in the environment, or at least the same "unknown factors" operated under laboratory as under natural conditions.^(a)

2. Effects on Aquatic Biota

Most of the research information on *effects* of fission products and other components of fallout on aquatic organisms has perforce been by laboratory experiment. Fortunately, except for a few local areas (see chapter 12), concentrations in the aquatic environment did not reach levels that would deliver significantly deleterious doses. Most of the early work addressed fish, their eggs or embryos, and used external x-ray or gamma-ray sources as described in chapter 11. We might add that succinct summaries can be found in the chapters by Donaldson and Foster (1957) and Krumholz and Foster (1957) in the NAS-NRC report cited in the previous section.

Work with radionuclides in water was not reported with any regularity until the late 1950s, except for the early reports on goldfish done at the Metallurgical Laboratory by Prosser (1945) and Prosser, Hagen, and Grundhauser (1947). For many years, the reports came primarily from the USSR, the United Kingdom, and Japan. The results were brought together in an important report prepared by panels of the IAEA that met periodically from 1970 to 1974 (IAEA 1976). Table 13.11 gives a more or less chronological overview of the work done, arranged by radionuclide and showing the organisms tested, the concentrations studied in the experiments, and the effects seen or looked for but not seen.

The concentrations at which positive effects appear are sometimes quite low and hark back to the admonitions of Polikarpov cited in chapter 12. It would be a major undertaking to calculate the associated radiation doses, and even if these were calculated, we could not be sure of their adequacy. Suffice it to say that the investigators did not find major differences in apparent radiosensitivity between the aquatic organisms tested and the more commonly studied terrestrial forms. It should be realized that much of the work involved eggs or

(a) This should not be interpreted as indicating that better data and greater consistency did not result from the laboratory studies; only that the differences continued to be real and were not wiped out universally by the "controlled experiment."

TABLE 13.11. Summary of Experimental Studies on the Effects of Radionuclides in Water on Aquatic Organisms


























		(Positive Effect: ● or ) (Negative Effect: ○ or )							
		Concentration of Radionuclides * ($\text{Ci} \cdot \text{l}^{-1}$)							
Investigators		10^{-12}	10^{-10}	10^{-8}	10^{-6}	10^{-4}	10^{-2}	1	Types of Effects
1958. Lebedeva, Sinevid	^{90}Sr ^{90}Y								Shortened the life-span of adult individuals of <i>Daphnia magna</i>
1958. Telichenko									Delay in embryonic development of fish eggs (anchovy)
1961. Polikarpov, Ivanov	^{90}Sr ^{90}Y								Increase in the mortality rate of embryo of fish eggs and tendency to be smaller in size of young fish was observed
1962. Polikarpov, Ivanov	^{90}Sr ^{90}Y								Decrease in cell division in gastrula stage and chromosome aberration of fish eggs (anchovy, stone perch)
1962. Polikarpov, Ivanov	^{90}Sr ^{90}Y								Increase in malformation rate of fish eggs (anchovy, mullet, green wrasse, horse mackerel)
1964. Fedorov et al.	^{90}Sr ^{90}Y								Increase in malformation rate of fish eggs (plaice, <i>Pleuronectes platessa</i>)
1964. Brown, Templeton	^{90}Sr ^{90}Y								No significant increase in mortality or in the production of abnormal larvae (brown trout, <i>Salmo trutta</i>), (plaice, <i>Pleuronectes platessa</i>)
1966. Neustroev, Podymakhin	^{90}Sr ^{90}Y								The rate of development of the egg was the same as the control up to the stage of one-third development of the yolk sac (Atlantic salmon, <i>Salmo salar</i>)
1966. Kulikov et al.	^{90}Sr ^{90}Y								Morphological abnormalities, delay in development and mortality (eggs of the fresh water mollusc, <i>Lymnaea stagnalis</i>)
1968. Shekhanova, Pechkurenkov	^{90}Sr ^{90}Y								Non-developing larvae appeared in developing eggs of the loach
1970. Hiyama, Shimizu, Suyama	^{90}Sr ^{90}Y								Sharp decrease of the rate on attaining to pluteus stage (see urchins, <i>Pseudocentrotus depressus</i> , <i>Anthocardia crassispina</i>)
1970. Hiyama, Shimizu, Suyama	^{90}Sr ^{90}Y								Normal rate of hatching and malformation of eggs (<i>Mylio macrocephalus</i> and <i>Rudaris ercodes</i> in sea water)
1970. Egami et al.	^{90}Sr ^{90}Y								Normal rate of mortality and abnormality of the embryo (fresh water killifish, <i>Oryzias latipes</i>)
1970. Egami et al.	^{90}Sr ^{90}Y								Effect on gonad was found in fish, exposed in contaminated water, continuously 70 days after hatching (fresh water killifish, <i>Oryzias latipes</i>)
1970. Egami et al.	^{90}Sr ^{90}Y								Damage on seminal glands in fish, exposed 15-30 days (fresh water killifish, <i>Oryzias latipes</i>)
1973. Kosheleva	^{90}Sr ^{90}Y								Egg mortality during the time of incubation was at the control level in the Atlantic salmon (<i>Salmo salar</i>)
1972. Nelson	^{90}Sr ^{90}Y								Significant increases in abnormal larvae (Pacific oyster, <i>Crassostrea gigas</i>)
1972. Tsytugina	^{90}Sr ^{90}Y								Significant increase of chromosomal breakages was found in the ruff (<i>Scorpaena porcus</i>)
1971. Guthrie and 1973. Brust	^{90}Sr ^{90}Y								The testes and ovaries of adults were atrophied when larvae of <i>Aedes aegypti</i> and <i>A. atropalpus</i> were reared in radioactive water
1972. Scott									No significant differences on rainbow trout during embryogenesis
1973. Strand et al.	^{90}Sr ^{90}Y								No decrease in the percentage of dividing cells was detected in the investigated development stages. In variants with $2 \times 10^{-8} \text{ Ci} \cdot \text{l}^{-1}$, there was a reliable increase in the frequency of chromosomal aberrations, beginning with the epithelial blastula stage (<i>Salmo salar</i>)
1973. Migalovskaya	^{90}Sr ^{90}Y								No influence on population density in a population of a copepoda (<i>Tigriopus californicus</i>) kept in radioactive water for several years
1965. Williams, Murdoch	^{137}Cs								No visible abnormalities on the developing eggs and larvae (mummichogs, <i>Fundulus heteroclitus</i>)
1967. White et al.	^{137}Cs								No effect on the reproduction of <i>Artemia salina</i>
1969. Hallopeau	F.P., ^{137}Cs								

TABLE 13.11. Continued.

		(Positive Effect: ● or ) (Negative Effect: ○ or )								
		Concentration of Radionuclides * ($\text{Ci} \cdot \text{l}^{-1}$)								
Investigators		10^{-12}	10^{-10}	10^{-8}	10^{-6}	10^{-4}	10^{-2}	1	Types of Effects	
1973 Kosheleva	F.P., ^{137}Cs								Considerable number of deaths were observed in the Atlantic salmon (<i>Salmo salar</i>) when the eggs were exposed to radioactive water	
1973 Migalovskij	^{144}Ce									
1971 Mashneva	F.P.								Damage at early stages of developing eggs of carp and <i>Coregonus peled</i>	
1972 Nelson	^{61}Cr or ^{66}Zn								Significant increases in abnormal larvae (Pacific oyster, <i>Crassostrea gigas</i>)	
1973 Havlik, Robertson	^{226}Ra								Photosynthetic oxygen production in fresh-water phytoplankton was sharply reduced by 24 hours exposure to a ^{226}Ra concentration of $3 \times 10^{-8} \text{ Ci} \cdot \text{l}^{-1}$	
1970 Akita, Shiroya	HTO (tritiated water)								50% attainment to pluteus (red sea urchin, <i>Pseudocentrotus depressus</i>)	
1970 Akita, Shiroya	HTO (tritiated water)								50% attainment to pluteus (violet sea urchin, <i>Anthrocidaris crassispina</i>)	
1970 Etoh, Ueno, Ichikawa	HTO (tritiated water)								Slight decrease of the rate of hatching (fresh water killifish, <i>Oryzias latipes</i>)	
1969 Buggeln, Held	HTO (tritiated water)								Reduced percentage of germination of the asexually produced spores (<i>Padina japonica</i>)	
1970 Blaylock et al	HTO (tritiated water)								No effects on embryo development of <i>Cyprinus carpio</i>	
1973 Walden	HTO (tritiated water)								No effects on embryo development of <i>Gasterosteus aculeatus</i>	
1973 Erickson	HTO (tritiated water)								No significant effect on mortality growth, male characters, behaviour and thermal death of the guppy fish, <i>Lebistes reticulata</i>	
1974 Ichikawa, Suyama	HTO (tritiated water)								Decreases in hatchability were observed and $10 \text{ Ci} \cdot \text{l}^{-1}$ effects were noted on body shape and eye diameter of larvae of two species of marine fish (<i>Paralichthys olivaceus</i> and <i>Fuguiphobies</i>)	
1972 Fedorova	^{14}C								Increase of malformed larvae of <i>Coregonus peled</i> , when $\text{NaH}^{14}\text{CO}_3$ was added to the water seven days after fertilization	
1972 Tsytugina									Significant increase of chromosomal breakages was found in the ruff (<i>Scorpaena porcus</i>)	

Note: * It is important to realise [sic] that the quoted concentrations do not indicate directly the dose received by organisms and/or organs.

Source: Modified slightly from IAEA 1976. See original for citations in the table.

embryonic stages of development of the aquatic forms and should thus be compared to developmental stages of terrestrial organisms.

The broad review by Rice and Baptist (1974) already mentioned gives a tabular summary of the radiosensitivity of aquatic organisms in terms of LD_{50} doses. Since it concerns only x- and gamma radiation from external sources, the table is not reproduced here but should be useful to those interested.

In addition to the processes listed in table 13.11, there have also been studies on genetic effects in aquatic forms (with equivocal results), the possibilities for repair of radiation damage, behavioral and metabolic stimulation, and environmental factors of importance in determining effects.

Included in the same IAEA report is detail on a chronic feeding experiment with yearling rainbow trout performed at Hanford over a several-year period. The results are shown as table 13.12:

TABLE 13.12. Effect of Chronic Ingestion of ^{32}P , ^{90}Sr - ^{90}Y , or ^{65}Zn on Yearling Rainbow Trout, *Salmo gairdneri*. Work at Hanford.

	Treatment $\mu\text{Ci}\cdot\text{g}^{-1}$ fish (day)	Duration of feeding (weeks)	Growth depression	Significant mortality	Leucopenia	Gut damage	Concentration at end of feeding ($\mu\text{Ci}\cdot\text{g}^{-1}$ wet)	
							Bone	Muscle
^{32}P	0.006	25	no	no	no	no	—	—
	0.06	25	wk 17	no	4 months	no	1.8	0.23
	0.60	25	wk 17	yes	17 days	yes	—	—
^{90}Sr - ^{90}Y	0.005	21	no	no	no	no	2.1	0.002
	0.05	21	no	no	no	no	26	0.078
	0.50	21	wk 12	wk 15	wk 15	yes	246	0.27
^{65}Zn	0.01	17	no	no	no	no	—	—
	0.10	17	no	no	no	no	—	—
	1.0	17	no	no	no	no	4.0	0.35
	10.0	10	no	no	wk 10	no	—	—

Note: References are: Watson, George, and Hackett 1959; Nakatani and Foster 1963; Nakatani 1966. Source: Modified from IAEA 1976.

Growth depression, leucopenia, gut damage, and significant mortalities were seen in trout fed $0.5 \mu\text{Ci } ^{90}\text{Sr}$ - ^{90}Y per gram daily for twenty-one weeks (a fairly large dose). Levels of 0.05 and $0.005 \mu\text{Ci/g}$ did not produce effects that could be measured. Phosphorus-32 was equally, if not slightly more, effective, while ^{65}Zn produced only leucopenia at the highest dose. If one considers that the highest dose resulted in levels of body burden of over 2,200 μCi of ^{90}Sr - ^{90}Y in a trout weighing 300+ g, we must be impressed by the relative radioresistance of these fish. However, truly long-term effects were not investigated.^(a)

The IAEA panels concluded that the most radiosensitive aquatic organisms are teleost fishes, particularly developing eggs and young of certain species. The most important effects are those that might operate at the population level such as fertility, fecundity, development, etc., but it seemed clear from the researches reported and the conclusions of the expert panels that doses needed to bring about significant changes would be moderately high, considerably above anything present in the current ambient environment. Thus, the research did not materially alter the conclusions from the environmental work quoted in chapter 12. However, it made them more secure.

Despite this relatively optimistic conclusion, it is not difficult to find large areas of aquatic biology that would benefit by more extensive and more penetrating research efforts on effects of radionuclides.

C. Plants and Plant-Soil Interrelationships

Research on the uptake, translocation, and retention of fission products and actinides by plants of many kinds began well before fallout occupied center stage. It was carried out primarily around the major production sites, Hanford

(a) The stimulus for long-term follow-up did not spread rapidly from the terrestrial animal realm to aquatic forms.

and Oak Ridge. The field work was described in chapter 11, and the fact that controlled laboratory work was needed and done was alluded to. In a previous section of this chapter, the role of early research at Hanford on plants in connection with the metabolism of pairs of elements was described. All of this, as well as the later work at the Savannah River facility, merged gradually into the developing research programs aimed at the problems of fallout. Since the projects form a continuum, it is difficult to earmark given pieces of work as having been directed specifically toward the problems of fallout. Therefore, we will discuss the pertinent work that could apply to fallout problems without splitting hairs regarding its motivation.

The U.S. installations most involved in either kinetic studies or work on effects, or both, include in addition to Hanford, Oak Ridge and Savannah River, the U.S. Department of Agriculture, University of California at Los Angeles and at Berkeley, Los Alamos, Brookhaven, and the UT-AEC Farm. There was also significant work abroad, especially in the United Kingdom and the Soviet Union. We will consider first some of the earlier work that more or less set the pattern and then studies that applied respectively to soil and soil chemistry, soil-plant interrelationships and distribution within plant parts, foliar deposition and absorption, and biological effects. In each case, we will attempt to identify contributions with the laboratory of origin.

1. Earlier Work

Probably the first identifiable reports on the behavior of fission product isotopes and actinides in plants came from the work of Jacobson and Overstreet at Berkeley during the Manhattan Engineer District (MED) days. This concerned uptake of several elements by the roots of barley and dwarf pea plants. The reports, produced first as an in-house document of the MED in 1945, and in 1947 as a publication in the open literature, were discussed briefly in chapter 6. The phenomena of ion exchange were just beginning to be utilized in ion exchange resins elsewhere in the MED and may have influenced the thinking on plant exchanges, although it could have easily been vice versa. At any rate, exchange reactions and metabolic processes were considered seriously. This early plant work pointed to the presence of similar exchange phenomena in the soil.

In the early 1950s, the Hanford annual reports began to carry periodic items on the uptake and translocation of fission products by plants (see, for example, Rediske and Selders 1952; Rediske, Cline, and Selders 1955).^(a) The plants were cultivated in nutrient solutions that were continuously aerated. Strontium-90, ^{90}Y , ^{137}Cs , and ^{131}I were added as tracers to the nutrient solutions. Uptake to beans was found to be proportional to concentration over a wide range. The accumulation of yttrium and iodine increased with increasing acidity, but that of cesium was little affected by pH, while that of strontium decreased with increasing acidity. Explanations were based on the tendency (or lack of it) for insoluble particles or complexes to be formed. Differences were found among species as just described for aquatic organisms. It was marked with cesium and yttrium, not so marked with strontium. Bean and tomato were consistently more efficient in taking up the radionuclides than wheat or Russian thistle. In none of the species did the fruit concentrate any of these four isotopes to any marked degree.

(a) The second reference cites several other progress reports issued in the intervening years.

In the 1955 Hanford report, ^{140}Ba , ^{106}Ru , and ^{239}Pu were added to the isotopes listed above. Concentration factors (leaves/soil) were determined for several soils and several species. Those for strontium were always the highest for barley, but for some other species that for ^{137}Cs was comparable or even a little higher. These relatively pioneering data are shown in table 13.13A and B.

TABLE 13.13A. The Concentration Factor (Conc. of Isotope in Leaves/Conc. of Isotope in Soil)* of Several Isotopes as Determined by the Neubauer Seedling Test Using Barley Grown in Representative Soils

Part 1.				
Soil	pH	% Organic Matter	Cation Exchange Capacity m.e./100g	
Ringold Silty Clay	7.6	7.9	34.1	
Wheeler Silt Loam	7.7	4.3	4.8	
Ritzville Very Fine Sandy Loam	7.8	3.0	5.2	
Sagemoor Very Fine Sandy Loam	8.2	2.8	7.1	
Ephrata Loamy Sand	7.3	1.8	8.1	
Warden Loamy Very Fine Sand	7.7	2.7	6.0	
Ephrata Fine Sandy Loam	7.5	1.9	4.4	
Quincy Sand	7.3	2.0	3.5	
Winchester Fine Sand	7.4	2.4	3.4	
Hanford Fine Sandy Loam**	6.6	1.45	8.2	
Aiken Clay Loam**	5.7	4.15	18.3	
Vina Fine Sandy Loam**	6.5	0.48	14.3	
Egbert Muck**	3.9	32.35	68.2	

Part 2.											
Soil	Isotope										
	Sr ⁹⁰	Ba ¹⁴⁰	I ¹³¹	Ca ¹³⁷	Y ⁹¹	Ru ¹⁰⁶	Ce ¹⁴⁴	Zr ⁹⁵ -Nb ⁹⁵	Pu ²³⁹	Pm ¹⁴⁷	
Ringold Silty Clay	.96	.13				.0083					
Wheeler Silt Loam	1.61			.037		.012	.0041	.019			
Ritzville Very Fine Sandy Loam	1.16										
Sagemoor Very Fine Sandy Loam	1.05					.0097					
Ephrata Loamy Sand	1.7		1.05	.10	.006	.015			.0009		
Warden Loamy Very Fine Sand	2.48					.0098					
Ephrata Fine Sandy Loam	2.02					.012					
Quincy Sand	4.46										
Winchester Fine Sand	3.05	.32		.076		.012	.0038	.0039		.0013	
Hanford Fine Sandy Loam**	2.22			.18	.003	.008	.002				
Aiken Clay Loam**	.96			.01	.004		.001				
Vina Fine Sandy Loam**	.79			.006	.006	.002	.003				
Egbert Muck**	.81			.12	.003	.012	.007				

*Values are based on dry weights of leaves and soil. If wet weights are used the concentration factor will be about one-tenth of that given.

**The data for the last four soils were obtained from Document UCLA-282 and are expressed as per cent of total dose absorbed by the aerial portions. This is closely comparable to the concentration factor for the Neubauer seedling test.

TABLE 13.13B. The Nutrient Solution. Concentration Factors for Several Fission Products and Plutonium. The pH of the nutrient environment was 6.0, with 1.0 μg of carrier/ml in all cases except Pu^{239} , when a concentration of $2.2 \times 10^{-4} \mu\text{g}$ of the isotope was used per ml of solution.

Plant	Concentration Factor						
	Sr^{90}	Cs^{137}	Y^{91}	I^{131}	Ru^{106}	Ce^{144}	Pu^{239}
Bean							
Leaves	.3	.7	.0005	.3	.0002	.001	.0003
Pod and Seeds	.02	.2	.00004	.04			
Tomato							
Leaves	.4	.3	.002	.2	.0002	.0001	.0002
Fruit	.009	.2	.0009	.02			
Russian Thistle							
Leaves and Stem	.1	.05	.00006	.5	.0002	.0002	.00002
Fruit	.008		.000003	.4			
Grasses							
Barley							
Leaves				.5	.0001	.00007	.0002
Wheat							
Leaves	.3	.02	.00003				
Head		.01	.000005				

Source: Modified slightly from Rediske, Cline, and Selders 1955.

Thus, we see again that the patterns of uptake are element-specific and species-specific and considerably affected by the composition of the medium, in this case soil. Note that in only a few instances are the concentration factors for these plants higher than unity. In general, they were well below unity, quite in contrast to those we saw for aquatic biota in table 13.10. The radionuclides are much less available from soil than from water.

This early Hanford work was presented, in part, at the first Atoms for Peace Conference in Geneva (Rediske and Hungate 1956). Considerable point was made there of the increase in absorption with increase in concentration.

Meanwhile, comparable pioneering experimental work was being done by the budding radioecology group at Oak Ridge National Laboratory (see chapter 11).^(a) We saw some of their work involving inoculating trees, and their survey work on the White Oak Lake bed in chapter 11. A more or less typical example of their attack on some of the problems just described can be seen in work by Auerbach and Crossley (1958), which was summarized at the second Atoms for Peace Conference in Geneva, Switzerland. It did not utilize nutrient solutions but used instead the natural soils of the White Oak Lake bed. Since specific crops were grown in specific plots, and a careful experimental pattern was applied, the work can still be classified as research. This work did not report concentration factors, partly because the base-line for the soils was rather tenuous. They showed real differences among the parts of plants and very large differences among the isotopes measured. These are illustrated in table 13.14.

The Oak Ridge work, like that described above, indicated discrimination factors near unity, with some variation among plant parts. They also studied the

(a) Plant work at the UT-AEC farm came somewhat later.

TABLE 13.14. Work on Corn Grown in White Oak Lake Bed, Oak Ridge, Tennessee. Mean Concentrations of Elements^(a) in *Zea mays*.

Element (per 100 g)	Leaf	Husk	Grain	Cob	Stem	Flower	Least significant difference
Sr ⁹⁰ (10 ⁻³ μ c)	39.7	6.3	2.5	4.4	12.1	28.4	11.00
Cs ¹³⁷ (10 ⁻³ μ c)	49.1	21.9	12.7	19.5	17.1	69.1	6.38
K (g)	1.54	0.98	1.21	0.94	0.67	0.64	0.25
Ca (g)	0.568	0.111	0.107	0.0568	0.165	0.228	0.047
Na (g)	0.0133	0.0049	0.0041	0.0034	0.0028	0.0054	0.0041
P (g)	0.163	0.153	0.174	0.154	0.186	0.071	0.056
Mg (g)	0.166	0.0656	0.0707	0.0437	0.0895	0.111	0.041

(a) Dry weight basis.

Source: Modified slightly from Auerbach and Crossley 1958.

strontium/calcium ratios and found relatively little discrimination against strontium, even though the calcium level in the soil (corn plot) was moderately high. Later work at the UT-AEC Farm on field crops yielded comparable results.

This work with plants led to the same emphasis on strontium as the key radionuclide from the standpoint of hazard as came out of the animal experiments. Although the concentration factors were all much lower than in animal or aquatic systems, strontium was, in general, at or near the top in actual concentration. Besides, it had a long half-life and a low maximum permissible concentration (MPC) in humans. It cannot be said that the high uptakes and retention of strontium were expected to the same extent as in animal systems with their large bony structures. Indeed, it might have been expected that plant systems would show a different pattern, particularly in research where individual variables could be controlled. But they did not.

2. Concentration of Plant and Soil Work on Fallout Problems

While the earlier work was clearly applicable to the radionuclides in fallout, it was quite general in purpose. As the fallout controversy heated up, more and more research on plants and soils was overtly correlated with it. Experimental work was done in many more laboratories than took part in the earlier work. Among these was the Atomic Energy Project at UCLA whose involvement with weapons testing we have already seen. The University of California, Los Angeles, began greenhouse experiments very early, and even now some residuals of the work continue to be reported. Work on soil also expanded. In addition to UCLA and Hanford, the laboratories included Los Alamos, the USDA, and laboratories in the United Kingdom and the Soviet Union.

While the research forms a continuum, it is useful to segregate our discussion and consider in turn soils per se, soil-plant interrelations and movement within plants, the role of foliar deposition and absorption, and finally, effects.

a. Soils

It was soon apparent, as the data in table 13.13A showed, that soil type could exert a large influence on plant uptake. Research on what was going on in the

soil attracted chemists and agronomists. The idea of fixed versus exchangeable portions of the soil constituents is threaded throughout the research (note, for example, the inclusion of "cation exchange capacity" for the soil types listed in table 13.13A).

A handy compendium of what earlier research on soils in various laboratories was revealing is found in the first four papers in the Minnesota symposium. Alexander, Hardy, and Hollister (1960) from the USDA, HASL, and AEC Headquarters, respectively, put special emphasis on strontium in soil at a variety of locations. This was mostly observational, but the effects of depth, amount of precipitation, and other environmental factors were investigated. The next paper concerning work done at Berkeley (Hanson, Vidal, and Stout 1960), considered the physicochemical composition of soil and its influence on the behavior of both naturally occurring and manmade radioisotopes. Menzel (1960), from the USDA, studied the effects of soil amendments on availability of various isotopes. Addition of lime, gypsum, fertilizers or organic matter, in reasonable doses, had only moderate effects on availability of ^{90}Sr . The effects were larger on some of the other fission products, but the importance of these was smaller because of the lesser hazard of the radionuclides concerned (i.e., ^{137}Cs , ^{144}Ce , and ^{106}Ru).

The fourth paper in the soil series, also from the USDA, included much about soil-plant interrelationships (Fried and Heald 1960). It provided insight into the general thoughts about soil mechanisms, including the idea that there were ions in solution in soil, ions fixed by chemical bonding, and ions attached to particles by adsorption. The relative contribution of each of these is influenced greatly by conditions such as pH, concentration of the elements, presence of other elements, differences in anions, etc.

Consideration of and research on the state of radionuclides in soil permeates much of the UCLA ecological work beginning with the early reports on the Trinity site (chapter 12). There were many observations on the relative fixation of different radionuclides. Laboratory work was reported as early as 1953. Neel et al. (1953) studied five isotopes, ^{90}Sr , ^{137}Cs , ^{106}Ru , ^{144}Ce , and ^{90}Y , in five different California soils. In further work, the fractions in soil of water-soluble nonexchangeable ^{90}Sr , ^{89}Sr , ^{91}Y , ^{106}Ru , ^{137}Cs , and ^{144}Ce were measured in a laboratory experiment and found to be quite different from each other (Nishita, Kowalewsky, and Larson 1954). Interestingly, the exchangeable fraction of ^{89}Sr was found to be greater than that of ^{90}Sr (mechanism?) and both of these were higher than ^{137}Cs and much higher than the other nuclides. The reverse was, of course, true for the nonexchangeable fraction.

A good review of this and related work at UCLA with soils and plants can be seen in a summary report (Nishita and Larson 1957). Other research at UCLA bearing primarily on soil reactions concerned the influence of stable cesium and potassium on the reactions of ^{137}Cs and ^{42}K in soils and clay (Nishita et al. 1959, 1960), reactions of tungsten in soil and its uptake by plants (Romney and Childress 1961), and a general review in 1965 (Nishita, Romney, and Larson 1965). There was also some work on chelation (see next section), and work on plutonium in soils. It began, as we have seen, in connection with the studies around the Trinity site; but true research came considerably later.

Research on the relative exchangeability and nonexchangeability of ^{90}Sr in soil and its importance to plant uptake was followed further at the Department of Agriculture (Roberts and Menzel 1965). This was a greenhouse experiment with four soil types obtained from North Carolina. The percent of

nonexchangeable ^{90}Sr varied from 11.9 to 50.3, a not inconsiderable factor to reside in the soil alone.^(a)

Probably the "purest" research involving interactions of radionuclides and soils came after the peak of activity in fallout research. It was concerned more with the problems of nuclear waste disposal and included the actinides to a greater extent than earlier work. Details are beyond our purview here. However, a glimpse of the kinds of work done can be gleaned from the first five papers in a special issue of *Soil Science* (132(1) July 1981) devoted to a multi-laboratory endeavor^(b) on radionuclides in soil. The five papers are listed below:

1. "The Interactions of Low-Level, Liquid Radioactive Wastes with Soils: Behavior of Radionuclides in Soil-Waste Systems." E. B. Fowler, E. H. Essington, and W. L. Polzer.
2. "The Interactions of Low-Level, Liquid Radioactive Wastes with Soils: Differences in Radionuclide Distribution among Four Surface Soils." E. H. Essington, E. B. Fowler, and W. L. Polzer.
3. "The Interactions of Low-Level, Liquid Radioactive Wastes with Soils: Interaction of Waste Radionuclides with Soil from Horizons of Two Soil Series." W. L. Polzer, E. B. Fowler, and E. H. Essington.
4. "Effect of Soil Type on the Extractability of ^{237}Np , ^{239}Pu , ^{241}Am , and ^{244}Cm as a Function of pH." H. Nishita, A. Wallace, E. M. Romney, and R. K. Schulz.
5. "Some Factors That Influence the Extractability of ^{239}Pu from Several Clay Minerals." H. Nishita and R. M. Haug.

The first three papers were from the Los Alamos National Laboratory, the other two were from UCLA (Laboratory of Nuclear Medicine and Radiation Biology, new name for the old Atomic Energy Project).

The types of complexing and various mechanistic aspects were emphasized. It was clear that the research showed considerably more sophistication in understanding the interactions of radionuclides with various soil components than in the 1950s and 1960s.

As part of the series of reports on fallout prepared by the NAS-NRC in the mid-1950s and early 1960s, known as the BEAR reports and cited in earlier chapters, there was one on the behavior of radioactive fallout in soils and plants. This review (NAS-NRC 1963) was prepared by M. H. Frere and R. G. Menzel from the USDA; Kermit Larson from UCLA; Roy Overstreet from the University of California, Berkeley; and R. F. Reitemeier, a soil scientist with the AEC Division of Biology and Medicine. In its survey section on soil reactions, the several processes were described briefly. A few general comments can be made:

- a. Because of the very low concentrations involved, adsorption of most of the ions of importance to fallout studies was found to be nearly complete. It would fall off at concentrations above about 0.01 times the saturation capacity of the soil.

(a) The fractions varied in different years; those given are for 1955. The range was lower in 1958.

(b) University of California at Los Angeles and at Berkeley, Los Alamos, and Savannah River.

- b. Removal (i.e., desorption) is difficult and may require very large volumes of water. Nevertheless, there is gradual leaching of the more mobile materials such as ^{106}Ru and ^{106}Rb to lower strata. Strontium is leached more slowly, while cesium and plutonium are still more tenaciously held.
- c. Complementary ions exert strong effects on adsorption. The order of replacement of soil materials is usually $\text{Li} < \text{Na} < \text{K} < \text{NH}_4 < \text{Rb} < \text{Cs} < \text{H} < \text{Mg} < \text{Ca} < \text{Sr} < \text{Ba} < \text{Fe} < \text{Al} < \text{La}$. No single exchange reaction appears sufficient to account for the phenomena.
- d. The effect of pH is not simple. High acidity or alkalinity result in decomposition of soil minerals, and less fission product adsorption occurs. Maximum adsorption of strontium seems to occur at pH 7 and 9, of cesium at pH 6 and above, of yttrium and cerium above pH 6 and of plutonium from pH 2.5 to 9.0.
- e. Clay is unique in some of its capacities for exchange. There are differences among clays.
- f. Organic matter that can be decomposed can reduce the uptake of strontium by soil.
- g. Mechanisms exist for more or less permanent fixation of portions of the radioisotope content of many soils.
- h. A result of all this is that practically never is all the radioactivity resident in a given soil available for plant uptake.

While there was considerably more work done on soil-radionuclide interactions, it is so intimately bound up with plant uptake and mobilization studies that we will postpone further discussion to the next section.

b. Plant Uptake, Soil-Plant Interrelationships, Distribution in Plants

Programs at several American laboratories concentrated on plant uptake and subsequent phenomena before, during, and after the climax of the fallout problems. Early work has already been mentioned. Studies concerned with the major sites and the more purely observational work have also been described (in chapters 11 and 12). Foliar deposition will be considered as a separate entity. Is there anything left? Indeed there is, as we will see.

The UCLA project was a prime contributor to the experimental work that followed the earlier Hanford and Oak Ridge landmark studies.

It became evident from "glasshouse" studies that strontium uptake clearly exceeded that of ^{137}Cs and ^{106}Ru in several species of plants (Neel et al. 1953), while uptakes of ^{144}Ce and ^{91}Y were negligible, all in conformation to the field work. There was also expansion of work on the effects of pH, concentration of stable carrier, of other ions, and even of temperature (Ehrler, Lange, and Hamner 1955; Ehrler, Romney, and Hamner 1955; Lange, Ehrler, and Hamner 1955; Romney et al. 1956; Goss and Romney 1957; and summaries by Nishita, Romney, and Larson 1965; and Nishita and Larson 1957). These experiments confirmed, extended, and made more quantitative the general findings already presented for less controlled conditions. They usually used only one radionuclide at a time and, of course, tested several plant species, but only one at a time, usually under optimal conditions for growth.

There was interest in whether or not the events noted in a single-generation experiment would extend over successive generations. This was approached by growing clover through fourteen successive cuttings under the influence of application of a calcium amendment aimed at suppressing strontium uptake

(Romney et al. 1960). There was some change with time, partly because the soil was initially low in calcium.^(a)

Some of the research was aimed toward finding ways to decrease or even prevent the uptake of the most hazardous radionuclides. Much of the work on addition of calcium, potassium, etc., had this as an objective as much as the strontium/calcium ratio and mechanisms. A new approach to this was through the possible effects of chelating agents (see chapter 19 for the agents and their application to therapeutic removal of radionuclides from animals and humans). At UCLA, Essington, Nishita, and Wallace (1961) tried several such agents, e.g., DTPA, HEEDTA, EDDHA (see chapter 19). The uptake of ^{91}Y and ^{65}Zn was increased, not a surprising result if we regard the chelation process as a solubilization process. This effect was, of course, in the wrong direction for suppressing uptake.

In much later work on the actinide ^{241}Am , (Wallace et al. 1976) there was ample evidence that DTPA could increase plant uptake significantly. The result was a discrimination ratio for the radionuclide of as much as seven instead of the normal ratio of unity or below. There were differences in detail among plants. These results were of scientific interest, but somehow the converse experiment of seeing if chelating agents would hasten the elimination of radionuclides from plant parts, i.e., the approach used in the animal work, did not get done. However, it was noted that even the solubilized americium was not readily translocated to the reproductive parts of the plants.

One of the primary conclusions from the UCLA research was that no matter how conditions were changed, the isotope showing greatest uptake and greatest potential hazard via the plant chain still was strontium. Thus, again plants did not differ from animals. The low capacity of plants to take up ^{91}Y , ^{106}Ru , ^{137}Cs , ^{144}Ce , etc., placed these in the category of "nuisance factors" compared to ^{90}Sr (Romney et al. 1957). Furthermore, no practical manipulation of soil characteristics had really significant effects on plant uptake rates except when a deficient soil was brought up to normal content of, for example, calcium, potassium, etc., or the soil was relatively infertile (Romney et al. 1959).

Work at Los Alamos on plant uptake has already been noted in connection with discrimination against strontium versus calcium at various calcium levels (figure 13.13). As described, Adams, Christenson, and Fowler (1965) looked at the influence of depth of cultivation on uptake of ^{137}Cs . While there were species differences, there was no doubt that deeper cultivation increased the fraction absorbed. Indeed, very deep cultivation resulted in nearly complete absorption. This highlights again the very important difference between field and laboratory since it is common in the laboratory experiment to mix the radionuclide quite completely with the soil. Cultivation in the field seldom approaches complete mixing to the depth of many plant roots.

The researchers also looked in some depth at the deposition and retention of radionuclides in different parts of the plants. Some of the results can be seen in the reviews cited above. Leaves tended to accumulate the most on the average. Stems tended to be about half as active as leaves, and other parts were still lower. Roots were sometimes quite high, probably because of their direct contact with the elements in soil. An example of the range of distribution among

(a) Later work with plutonium showed more clear-cut changes with time, as we will see presently.

the parts of plants of seven species and for six isotopes is given in table 13.15, taken from UCLA work.

TABLE 13.15: Distribution of Fission Products in Different Parts of Crop Plants

Plant parts	Dose in Soil $\mu\text{C/kg}$	Radioisotope					
		^{90}Sr	^{137}Cs	^{106}Ru	^{144}Ce	^{91}Y	$^{95}\text{Zr-Nb}$
Maize					dis/sec/g		
leaves	243	4,683	—	5.0	16.7	—	—
stems		633	—	1.7	1.7	—	—
panicle		1,023	—	3.0	3.3	—	—
husk		220	—	0.3	1.7	—	—
cob		283	—	0.5	3.3	—	—
grain		18	—	0.17	—	—	—
Wheat							
leaves	156	11,422	63.3	—	11.7	—	—
stems		1,817	18.3	—	3.3	—	—
grain		638	10.0	—	1.7	—	—
Pea							
leaves	*	2,605	—	—	17.0	10.0	7.09
stems		1,904	—	—	3.68	1.55	2.30
pods		1,115	—	—	1.98	0.80	2.28
seeds		73	—	—	0.13	0.02	0.30
roots		3,530	—	—	662.0	385.0	418.0
Bean							
leaves	2.7	1,945	13	67	10	6	—
stems		1,002	7	3	3	2	—
fruits		320	13	6	3	2	—
Lettuce							
leaves	2.7	757	65	9	2	3	—
stems		424	29	2	1	1	—
Radish							
leaves		1,813	22	9	10	5	—
roots		455	21	4	6	7	—
Carrots							
leaves	2.7	910	20	73	2	4	—
roots		297	24	1	1	3	—

*Dose in soil ($\mu\text{C/kg}$): ^{90}Sr = 244, ^{144}Ce = 233, ^{91}Y = 216, and $^{95}\text{Zr-Nb}$ = 180.

Source: Reset from Nishita, Romney, and Larson 1965. Reprinted with permission of Elsevier Science Publishers, Amsterdam, copyright 1965.

Such distributions changed in an absolute sense but not relative to each other when the nutrients came from water cultures rather than soil (much higher counts in each part from the water culture).

The relative order of plant uptake of fission products and plutonium defined by these many laboratory experiments was $^{89-90}\text{Sr} > ^{131}\text{I} > ^{140}\text{Ba} > ^{137}\text{Cs}$ and at much lower levels $^{106}\text{Ru} > ^{144}\text{Ce} > ^{91}\text{Y}$ and $^{147}\text{Pm} > ^{239}\text{Pu}$.

Numerous mechanisms have been proposed for the uptake of ions. They are no different for the radionuclides in fallout than for general uptake processes in plants, except that all reactions are in the low concentration realm. Most mechanisms postulate the participation of a carrier compound or process. Some ions, e.g., calcium, strontium, and barium, seem to compete for an identical carrier, whereas others, e.g., potassium, rubidium, and cesium, compete for a different carrier (NAS-NRC 1957, p. 9). Translocation within the plant was greater for cesium, rubidium, and potassium than for strontium, calcium, yttrium, and other multivalent cations.

An interesting mechanism that can by-pass the soil reactions is absorption from the so-called plant base. This is the mat of roots, basal portions of stems, and organic matter on the surface of the soil. Experiments showed that absorption from this could be fairly large and that the process might account for some anomalously high strontium concentrations in pasture vegetation (NAS-NRC 1957, p. 11).

For more recent research with plant uptake, we turn to a short glimpse of the large and growing literature with the actinides. Much of the work was done at the same institutions we have been quoting, but there were also newcomers such as LLL, Colorado State, and others. A very useful compendium is the volume already quoted in other connections: *Transuranic Elements in the Environment*, edited by Wayne C. Hanson at Battelle, Pacific Northwest Laboratories (Hanson 1980). The synthesis of the research literature by many of the principal workers in the field (Watters et al. 1980) presents the results of many experiments on plant uptake and distribution in plants of the transuranics. Neptunium in valence V state was taken up to a much greater extent than plutonium, valence IV; americium, valence III; or curium, valence III. The relative uptakes were plutonium = 4, americium = 35, curium = 39, and neptunium = 3×10^4 . When solubilized to valence VI, plutonium was more readily absorbed, but it appears to revert to the IV state within the plant tissues and become less mobile again. Concentration ratios^(a) varied not only between plants and among elements, but they were different in experimental studies compared to field studies. In experimental studies, the concentration ratios for plutonium isotopes were 10^{-5} to 10^{-4} for native plants, 10^{-10} to 10^{-3} for agricultural crops; for ^{241}Am from 10^{-5} to 10^{-2} and 10^{-7} to 10^{-1} , respectively; 10^{-4} to 10^{-1} for ^{244}Cm ; and 10^{-2} to 10^{-1} for ^{237}Np in native plants.^(b) In field studies, the ratios tended to be about a factor of ten lower (Watters et al. 1980).

Does this result mean that some sort of solubilizing processes occur in the field? Yes. Such processes have been found by comparing sterile and microbially active soils in the laboratory. Wildung and Garland (1980) present evidence for microbial alteration of the solubility of plutonium in soil and enhancement of the uptake by plants. Changes in solubility with time and number of crops were described from Pacific Northwest Laboratory somewhat earlier (Vaughan 1974) but not specifically tied to microbial action. The answer seems to be that some of the relatively insoluble radionuclides may become more soluble with time, cropping, cultivation, etc.

(a) Transuranic concentration in receptor/transuranic concentration in donor.

(b) Agricultural crops appear not to have been studied in much detail with the latter three actinides. The ranges for these are so large that the apparent differences may be spurious. However, the investigators, with the full data at hand, concluded that there was a difference.

The transuranics were distributed more nearly uniformly in various plant parts than the fission products but with large differences among the elements. The seed persisted in having very little plutonium, americium, or curium, just as occurred with the fission products. However, there was considerably more ^{237}Np in seeds. A summary of these phenomena, taken from the review by Schreckhise and Cline (1980), is given as figure 13.18.

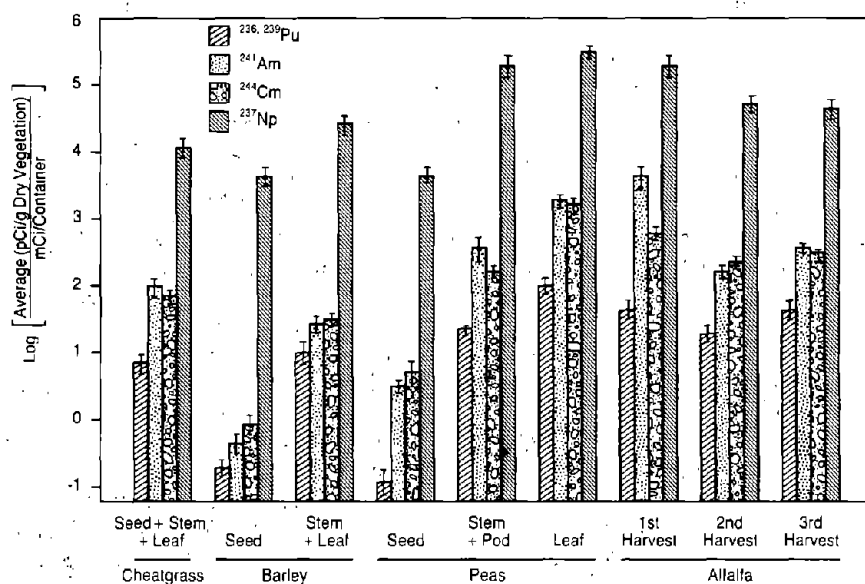


FIGURE 13.18. Uptake and distribution of plutonium, americium, curium, and neptunium. (Redrawn from Schreckhise and Cline 1980.)

We will close this section on plant uptake and distribution of the transuranics by listing the titles for most of the remaining papers from the special issue of *Soil Science* cited earlier. The University of California, Los Angeles, was a prime contributor to this work.

"Plant Uptake of ^{237}Np , $^{239,240}\text{Pu}$, ^{241}Am and ^{244}Cm from Soils Representing Major Food Production Areas of the United States." E. M. Romney, A. Wallace, R. K. Schulz, J. Kinnear, and R. A. Wood.

"Relationship between the Chemical Extractability of Several Transuranic Elements from Soils and Their Uptake by Wheat Plants." H. Nishita, A. Wallace, E. M. Romney, and J. Kinnear.

"Relative Adsorption and Plant Uptake of ^{238}Pu and ^{239}Pu in Soils." H. Nishita.

"Uptake and Translocation of Neptunium-237, Plutonium-238, Plutonium-239, 240, Americium-241, and Curium-244 by a Wheat Crop." R. K. Schulz and M. R. Ruggieri.

"Plutonium, Curium, and Other Radionuclide Uptake by the Rice Plant from a Naturally Weathered, Contaminated Soil." D. C. Adriano, K. W. McLeod, and T. G. Ciravolo.

"Uptake of Plutonium from Soils Contaminated by a Nuclear Fuel Chemical Separations Facility." K. W. McLeod, D. C. Adriano, and T. G. Ciravolo.

"Studies on Unsaturated Zone Hydrology and Radionuclide Migration at a Shallow-Land Burial Site." R. K. Schulz, E. B. Fowler, E. H. Essington, and W. L. Polzer.

"Effect of DTPA on Concentration Ratios of ^{237}Np and ^{244}Cm in Vegetative Parts of Bush Bean and Barley." E. M. Romney, A. Wallace, R. T. Mueller, J. W. Cha, and R. A. Wood.

"Effect of Concentration on ^{241}Am Uptake by Plants with and without DTPA Treatment." A. Wallace, E. M. Romney, R. T. Mueller, Sr., and S. M. Soufi.

"Plant Uptake and Transport of ^{241}Am ." A. Wallace, E. M. Romney, R. T. Mueller, Sr., and S. M. Soufi.

"Effect of Various Concentrations of DTPA Chelating Agent in Soil on Uptake and Distribution of ^{241}Am in Bush Bean Plants." A. Wallace, E. M. Romney, and R. T. Mueller.

"Frequency Distribution of ^{241}Am in a Population of Bush Bean Plants Grown in Soil in a Glasshouse." J. E. Kinnear, A. Wallace, and E. M. Romney.

Obviously, much of this later research bears on waste disposal problems, but it grew out of the problems of fallout and began with the problems of radioisotopes in the environment of the early atomic energy sites and thus is quite general in its applicability.

c. Foliar Absorption and Distribution Therefrom

It has been known since the 1930s that many substances in liquid or even solid form, in addition to gases, could be absorbed through plant leaves. This fact made interpretation of some of the fallout phenomena seen in the field tests easier, e.g., the phenomenon of plants with considerably higher contents of radionuclides than those measured in the surrounding soil. While some interpretations could be made by analyses on the test sites, more reliable information, particularly information pertinent to mechanisms, could be obtained under greenhouse conditions. Such work was done at nearly every laboratory having such facilities and an interest in plant uptake of fallout radionuclides. Frequently, the procedure was simply to apply an aerosol and then measure uptake and translocation. In other instances, variables were introduced that might bear on interpretation of mechanisms.

The NAS-NRC report of 1963 quotes UCLA work showing that most of the fission-product radioactivity associated with vegetation near NTS was in external dust and that mechanical trapping by hairs, glands, and stomata played an important role. Particles of less than $44\text{-}\mu\text{m}$ diameter were retained preferentially, while larger sizes were poorly retained (a general finding for other aspects of the NTS phenomenology—see chapter 12). Autoradiograms showed that strontium can enter directly through the intact epidermis of tomatoes (Martin 1954).^(a)

There were large species differences, dependent it would appear, on the degree of waxiness of the leaves. Retention and absorption by wheat plants was high (93% of applied cesium and 85% of applied strontium), while cabbage leaves absorbed only a few percent of the applied radioactivity. As a corollary, it was found easy to wash foliar depositions from some plants, almost impossible from others. These differed for different elements and, of course, the compound applied.

(a) This is not a universal finding for fruit.

The time in the growth cycle seemed to make a difference too. Absorption from foliar deposition was more rapid and larger if it occurred during periods of rapid growth. This implies a link of the processes, in part at least, to metabolic functions and is a general finding.

Biddulph (1960), from Washington State University, presented a reasonably complete review of foliar entry and distribution of fallout radionuclides and the mechanisms thereof at the Minnesota symposium cited many times. The processes are complex because leaf surfaces are complex. Briefly, there are two important phases: (1) exchangeable binding of ions to negatively charged biocolloids or to nondiffusible anions in the cell wall, and (2) active uptake into protoplasmic constituents of the cells. Specific ion-binding substances are postulated to take part in this process. If the element has no ionic partner, as is the case with many of the heavier fission products, it will not be taken into the cells and thus will remain in the axils of the leaves more or less indefinitely. Translocation of materials once absorbed is also quite variable among radionuclides. Some elements, such as divalent strontium, are largely immobilized within the leaf and accumulate in those leaves into which they are absorbed. Cesium, like potassium, is largely transported elsewhere after entering the leaf.

In the same volume, Middleton (1960), from the United Kingdom, details the very large contribution that foliar absorption can make and examines the influence of conditions but does not dwell much on mechanisms.

Investigators in the Department of Horticulture at Michigan State University became interested in the mechanisms of absorption of fission products by above-ground plant parts and presented a nice summary in the Fowler book (Bukovac, Wittwer, and Tukey 1965). They point to many similarities of the mechanisms of foliar absorption to those of root absorption. However, they are far from identical. This is illustrated by the relative rank of several fission products for foliar and root absorption and for redistribution, as shown in table 13.16.

TABLE 13.16. Classification of Certain Selected Fission Products as to Ease of Absorption by Foliage and Roots, and Redistribution Subsequent to Absorption

Process	Relative rank			
Foliar absorption	$^{137}\text{Cs} >$	$^{140}\text{Ba} >$	$^{89-90}\text{Sr} >$	^{103}Ru
Root absorption (soil)*	$^{89-90}\text{Sr} >$	$^{140}\text{Ba} >$	$^{137}\text{Cs} \approx$	^{106}Ru
Redistribution**	$^{137}\text{Cs} >>>$	$^{89-90}\text{Sr} >$	$^{140}\text{Ba} >$	^{103}Ru

*Data adapted from Nitschita et al.

** ^{137}Cs is readily redistributed from one plant organ to another, whereas, the others are not.

Source: Reset from Bukovac, Whitmer, and Tukey 1965. Reprinted with permission of Elsevier Science Publishers, Amsterdam, copyright 1965.

It is notable again that cesium is easily redistributed after foliar absorption, whereas strontium is quite immobile. The authors list several other ways in which foliar and root absorption differ^(a) and the many factors that may influence absorption by above-ground plant parts.

(a) In this as in many of the other research programs, distribution within the plant was demonstrated by autoradiography as well as by radiochemical analysis.

A full session was devoted to foliar absorption work at the Stockholm symposium on radioecological concentration processes (Åberg and Hungate 1967). Much of the work was from European laboratories. Kirchmann, Fagniant, and Van Puymbroeck (1967)^(a) from Mol, Belgium, used a motor sprayer to place artificial airborne contamination of radiostrontium or radiocesium on rye grass and red clover grown in pots. Their object was description of the influence of various factors on foliar retention. Radionuclide concentration had relatively little effect on the percentage retained. There was a small effect of the amounts of stable strontium or cesium on the $^{137}\text{Cs}/^{89}\text{Sr}$ ratio. The relation to plant yield seemed to be largely determined by geometry of the shoot or the nature of the cuticle. Moisture increased foliar retention in clover but reduced it in rye grass. Light intensity, surprisingly, had little effect, but temperature made considerable difference with uptake. It was greatly reduced by lowered temperature, and translocation essentially stopped below 21°C.

Merten and Buchheim (1967) from Kiel, West Germany, studied the influence of the microstructure of the plant surface on "fixation" of radiostrontium. The plants were dipped into solutions for periods from ten seconds to ten minutes and subsequent retention measured. Surfaces that were hydrophobic showed uptake capacities an order of magnitude lower than hydrophilic surfaces. In other work from Germany (Frankfurt), factors such as structure and arrangement of leaves and the density of standing growth were investigated (Nay 1967). The sparser the standing growth, the greater the contamination in a given plant. This seemed to have as much effect as species and structure.

Of considerable interest is work reported by C. F. Miller from the Stanford Research Institute in Menlo Park, California, on retention by foliage of silicate particles ejected by a volcano in Costa Rica (Miller 1967). Since much of the radioactivity deposited from fallout is in relatively insoluble form, such as silicates, this work is pertinent. It was largely observational. There was a large difference in contamination factors between this situation and foliar contamination in the weapons tests. Retention factors were as much as one-thousand times larger for the volcanic materials. It is suggested that the material from weapons tests had been subjected to more weathering. Retention under damp conditions was about twice that under dry conditions. The size distributions on the plants were about the same as in the ground, again in contrast to the classic 44- μm rule developed by UCLA (chapter 12) for NTS. It was again explained by longer weathering in the latter case.^(b) Menzel (1967) provided a different view of airborne nuclides and plants. This work took cognizance of the mechanisms of airborne transfer with and without rainfall (chapter 15), and it includes naturally occurring radionuclides such as radon and daughter products.

At an IAEA symposium in Vienna, the Oak Ridge group provided a very specific experiment with artificial fallout and a very specific crop, fescue. The abstract of this paper by Dahlman, Auerbach, and Dunaway (1969) gives some details:

(a) Another review of the same period was presented at a symposium of the AAAS, Agriculture and the Quality of Our Environment (Menzel 1967).

(b) The people at PNL interested in aerosols seized an opportunity to study fresh volcanic ash from the Mt. St. Helens eruption in 1980. Sanders, Gelman, and Conklin (1981) measured pulmonary retention and toxicity and concluded that the volcanic ash was essentially inert physiologically.

BEHAVIOUR OF ^{137}Cs -TAGGED PARTICLES ON A FESCUE MEADOW. Enclosures of tall fescue (*Festuca arundinacea*), 0.01 ha in area, were contaminated at the rate of 25 g/ft² using artificial fall-out (^{137}Cs fused to 88-177 μm silica sand, $\sim 100 \mu\text{Ci/g}$, 15% leachable in water) to study the effects of close-in fall-out on a grass system. Investigations of radiation effects, intercompartmental cycling of radiocaesium and secondary movements of the simulant particles in soil and litter have been in progress since mid-summer, 1968. Plant community response (yield, seed production and species composition), small mammal physiology (haemopoietic and gut effects) and insect population dynamics are being studied following exposure to chronic internal-external, beta-gamma radiation. Sand particles intercepted by grass blades were readily dislodged by light wind, and maximum retention time was approximately 10 days. The simulant was readily trapped in the leaf axils where it remained for 4 weeks until washed off by rain. There was significant transfer (15%) of ^{137}Cs from simulant to vegetation. Vacuum and brush cleaned vegetation initially contained 1.32 $\mu\text{Ci/g}$ (living parts) and 4.62 $\mu\text{Ci/g}$ (dead parts).

Early incorporation into foliage was largely by contact assimilation because appreciable uptake had occurred before the simulant had reached the soil. Two loss rates were evident in the subsequent decrease of ^{137}Cs in living foliage. The fast component, which began 8 days after contamination and continued for 4 weeks, was described by the linear regression $Y = 1.64 - 0.04X$ where Y and X are $\mu\text{Ci } ^{137}\text{Cs/g}$ foliage and days, respectively. The slower loss rate commenced 4 weeks after contamination and its regression was $Y = 0.61 - 0.003X$.

Only 0.12 mCi of ^{137}Cs (0.006 % of that present) was carried from the tagged areas in one runoff event. This agreed remarkably well with that predicted from a simple model based on characteristics of simulant and soil, and on rainfall-runoff relationships. (Dahlman, Auerbach, and Dunaway 1969)

While not particularly mechanistic, this experiment provides a good example of the relatively clean-cut information that carefully planned and executed field research can provide.

More work from abroad appeared in this symposium. The review by Keppel from the Federal Republic of Germany (Keppel 1969) gives a good comparison of the factors in roots and leaves that favor or inhibit absorption and makes it clear that these sometimes reinforce each other and sometimes work in opposite directions.

As expected, considerable research was done on the interaction of plutonium and other relatively insoluble actinides and plant foliage. This includes the role played by wind resuspension, details of which will be reserved for chapters 14 and 15.

A useful review of the general phenomena has been presented by Cataldo and Vaughan from PNL in the volume by Hanson quoted earlier (Cataldo and Vaughan 1980).^(a) The work shows that submicronic particle sizes are more effectively retained on plant foliage than are larger particles, that submicronic particles become less available for leaching with increasing residence time on the leaf, and that up to 90% of foliar plutonium deposits may be firmly held. A diagram of the glove box and miniature wind tunnel used for these Battelle studies (Klepper and Craig 1974) is shown as figure 13.19. The wind velocities in this experiment were very low.

(a) This followed earlier reports by Klepper and Craig in 1974 and a paper by Cataldo, Klepper, and Craig (1976), the latter giving considerable experimental information.

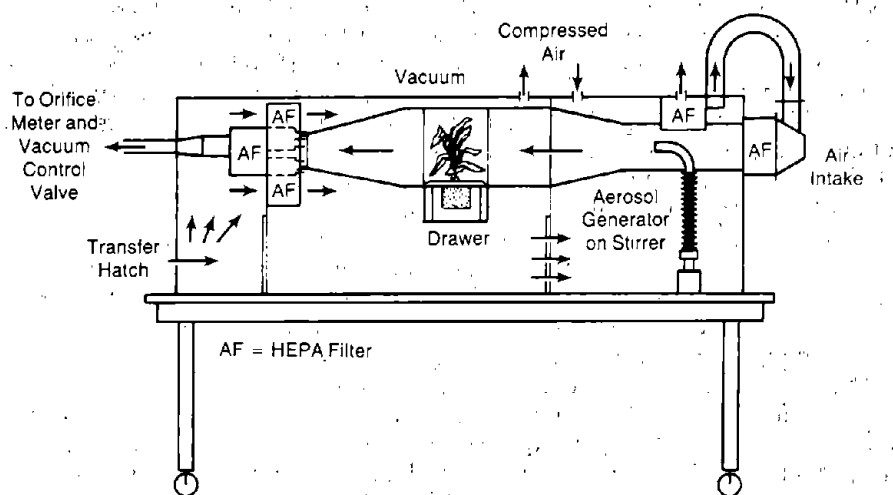


FIGURE 13.19. Transverse section of glove box and aerosol exposure wind tunnel. (Redrawn from Klepper and Craig 1974.)

Finally, lest we forget that plant leaves are freely permeable to gases such as oxygen and CO_2 , we should remark that a fairly considerable amount of work was done, much of it at the Savannah River Plant of AEC on tritium and tritiated water vapor. An example is research by Murphy and Corey (1976) in which branches of pine trees were enclosed in clear plastic bags containing tritiated water vapor. The conditions were such that all absorption would take place from the vapor phase. It was concluded that tritiated water vapor diffuses into foliage (of pine trees, at least) by the same pathway as water vapor diffuses out. It can be expected that tritium water vapor will be rapidly and completely exchanged in all plants.

The research on foliar absorption seems to have resulted in information more pertinent to botanical mechanisms than to the problems of fallout per se, except to prove in laboratory environments that foliar absorption of radionuclides can be very significant and that it is far from a simple process.

d. Effects on Plants

We discussed effects of radiation and radionuclides in ecosystems as part of chapter 11, and effects on animals have appeared in nearly every chapter. We saw in chapter 12 that descriptions have been given of the effects of fallout and also direct radiation on plants and plant communities on the Pacific atolls and at NTS. We also alluded earlier to the large experiments on plants with external radiation sources done at Brookhaven, Oak Ridge, Emory University, and elsewhere.

Radiation botany became a very active research area. Brookhaven was a mecca for this work, particularly because of the presence of Arnold Sparrow, George Woodwell, and many colleagues. It became the home base for a

journal, *Radiation Botany*, of which Sparrow was editor-in-chief for many years.^(a) Essentially all of the work utilized external sources of radiation.

At the unicellular and embryonic stages, plant and animal tissues have been found to react more or less similarly to radiation. At the more mature stages, higher plants show large differences from animal tissues. An excellent general summary of the type of work, the problems, and the findings can be seen in the chapter on plants in the text by A. P. Casarett (1968) already cited.

Work with the large field installations at Brookhaven and elsewhere showed that pine trees were relatively more sensitive than other trees. The doses to produce effects in higher plants were generally rather high, however. For this reason, very few attempts were made to do experimental effects research with radionuclides incorporated into plants. The potential contamination problems associated with such work were a strong deterrent.

The NAS-NRC report quotes some Russian work on metabolic effects from incorporated ^{90}Sr and ^{137}Cs and reduction of grain yield in wheat. The concentrations needed were 5 μCi of ^{90}Sr or 13 μCi of ^{137}Cs per gram of wheat. Resistance to radiation increased as the plants grew older. There was also some work with ^{32}P in young barley plants. The lowest-specific-activity level at which damage occurred was 170 μCi of ^{32}P per gram dry weight, and this damage was confined to the zones of active division (NAS-NRC 1957, p. 14, quoting work by Blume, Hagan, and Mackie 1950).

On the assumption that the effects of external radiation on plants apply in a general way to equivalent doses from deposited radionuclides, we can draw a few conclusions as to what effects research with these might show had it been done on a larger scale.^(b)

Three tables taken from the chapter by Casarett (1968) on the effects of radiation on higher plants and plant communities show the levels of dose associated with effects in plant communities and the predicted exposures required to produce from slight effects to LD_{100} (one hundred per cent kill) for a variety of plant species and communities.^(c) These are gathered together as table 13.17A, B, and C.

Remember that these data are all based on external radiation and that doses are expressed in roentgens (R). They confirm, as do data for individual plants and plant parts presented earlier in the same work, that higher plants are, in general, less radiosensitive than terrestrial animals. Since concentration factors for radionuclides in plants are not high, in general, these relationships can be expected to hold approximately also for the radionuclides from fallout.^(d)

It will be noted that table 13.17A and C contain information on chromosome volumes and number. This ties to what may be some of the most intriguing research on radiation effects in plants. This came from Brookhaven and work by Arnold Sparrow and his associates, especially George Woodwell. They made a systematic study of the doses required to produce growth inhibition under chronic exposure conditions, in a large number of plant species. There was an

(a) The journal operated from 1961 until December 1975 when it became *Environmental and Experimental Botany*, partly because of the untimely death of Dr. Sparrow.

(b) Much work was done with incorporated tritium as discussed in earlier chapters.

(c) A series of pertinent earlier papers is gathered in the First National Symposium on Radioecology.

(d) With the usual greater sensitivity of embryonic and growing tissues seen in all life forms.

TABLE 13.17A. Estimated Acute Exposures Required to Affect Dominants in the North American, Eastern Deciduous Hemlock-Hardwood Forest

Species	Somatic chromosome number	Interphase chromosome volume ($\mu^3 \pm \text{S.E.}$)	Sensitivity range: slight inhibition of growth to mortality (R)
<i>Tsuga canadensis</i> (hemlock)	24	21.3 ± 0.8	420-1,100
<i>Betula lutea</i> (yellow birch)	84	2.2 ± 0.1	3,860-10,120
<i>Pinus strobus</i> (white pine)	24	46.5 ± 2.8	190-500
<i>Pinus resinosa</i> (red pine)	24	43.2 ± 3.5	210-540
<i>Acer saccharum</i> (sugar maple)	26	3.2 ± 0.2	2,800-7,360

TABLE 13.17B. Estimated Radiation Exposures (R) Required to Damage Major Natural Communities

Communities	Level of damage		
	Minor	Intermediate	Severe
Coniferous forest	200	200-2,000	> 2,000
Deciduous forest	200	200-10,000	>10,000
Grassland	2,000	2,000-20,000	>20,000
Herbaceous annuals	4,000	4,000-70,000	>70,000

TABLE 13.17C. Predicted LD₁₀₀ Values and Acute Exposure Required to Produce Slight Effects on Vegetative Growth of Vegetable and Field Crops

Species	Estimated interphase chromosome volume ($\mu^3 \pm \text{S.E.}$)	Predicted exposures required to produce	
		slight effects (R)	LD ₁₀₀ (R)
<i>Allium cepa</i> (onion)	39.3 ± 2.3	377	1,491
<i>Triticum aestivum</i> (wheat)	14.6 ± 1.1	1,017	4,022
<i>Zea mays</i> (corn)	14.0 ± 0.6	1,061	4,197
<i>Solanum tuberosum</i> (potato)	4.6 ± 0.3	3,187	12,608
<i>Oryza sativa</i> (rice)	3.0 ± 0.1	4,974	19,677
<i>Phaseolus vulgaris</i> (kidney bean)	1.6 ± 0.1	9,137	36,149

Source: Reset from Casarett 1968, who had modified them from Woodwell and Sparrow 1965 for A and B and Sparrow et al. 1965 for C. Reprinted with permission of Prentice-Hall, Inc. Englewood Cliffs, New Jersey, copyright 1968, 1965.

excellent correlation between the average interphase nuclear volume and the daily dose required to produce severe growth inhibition. They covered twenty-three species of diploid cells with average nuclear volumes from 23 to 1,000 μ^3 , i.e., a factor of about fiftyfold. Another measure of the volume of nuclear material is ploidy. The higher plants show much more tendency to have cells with multiple ploidy than do animal cells. Sensitivity could be correlated with ploidy with greater sensitivity in the diploid state and less sensitivity as ploidy increased. Both of these phenomena are illustrated in figure 13.20A and B, taken from Sparrow and Woodwell (1963).

FIGURE 13.20A. Relationship between nuclear volume and daily dose rate required to produce severe growth inhibition in twenty-three species of plants chronically irradiated. (Redrawn from Sparrow and Miksche 1961. Reprinted with permission of Science, Washington, D.C., copyright 1961.)

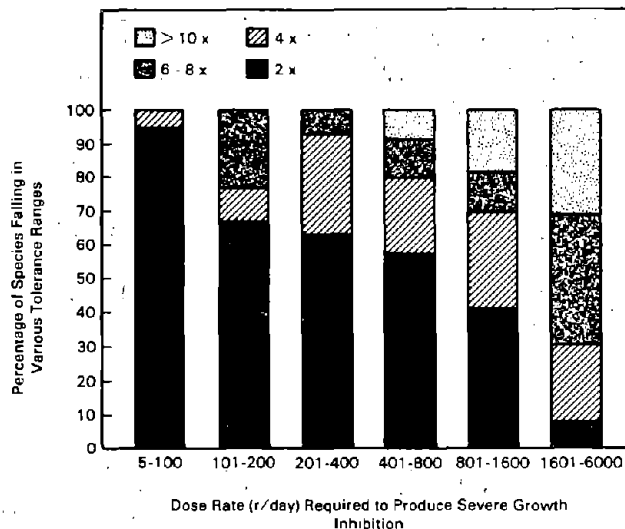
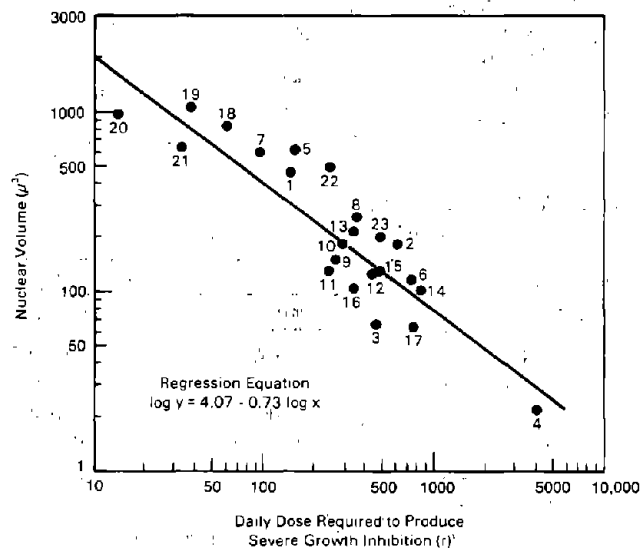


FIGURE 13.20B. Relationship between radiosensitivity and degree of polyploidy in 175 species of chronically irradiated plants. "X" in the legend refers to the ploidy of the group. (Redrawn from Sparrow and Evans 1961.)

On the basis of such correlations, Sparrow and Woodwell (1963) and Sparrow and Miksche (1961) were able to predict radiosensitivity of a large variety of higher plants.^(a) There is no reason to expect that the same general relationships would not hold for sensitivity to incorporated radionuclides.

Nevertheless, we must base our conclusions on the data at hand and derive ideas for effects of radionuclides by extrapolation from research with external radiation sources. The subject is still lively. A two-volume series edited by L'Annunziata and Legg (1984) considers many aspects of isotopes and radiation in agriculture. Evidently there are more volumes planned.

IV. Selected Radionuclides

This section is intended to highlight some of the results of the extensive research on the radionuclides present in fallout, with particular emphasis on those that have received the most attention, and thus can be considered as entities. We will emphasize that work most obviously associated with the problems of fallout per se, but for comparative purposes will include some work begun under the conditions described in chapter 8 before the fallout problems became of consuming interest. References will perforce be sparse except for summaries and some previously unreferenced documents. The bearing of the research findings on the possibility of *health effects from environmental exposures* will occupy our attention now.

A. Strontium

Of all the fission products, isotopes of strontium have received the most research attention by far. In addition to the general summaries already cited in this chapter (*Radioisotopes in the Biosphere*, 1960; *Radioactive Fallout, Soils, Plants, Foods, Man*, 1965; *Strontium Metabolism*, 1967; *Radioecological Concentration Processes*, 1967; *Biomedical Implications of Radiostrontium Exposures*, 1972; United Nations Scientific Committee 1977 and 1982, and the several national symposia on radioecology),^(b) the reader may also wish to consult the strontium reports for the Federal Radiation Council (FRC) (chapters 12 and 16), the BEAR reports (chapter 12), the several Hanford and Utah symposia discussed at length in chapter 8, and a small but succinct book edited by Engstrom et al. (1957). A relatively unknown but important summary concentrating on the pediatric significance of peacetime radioactive fallout was sponsored by the American Academy of Pediatrics (Pediatrics 1968). It provides a broad summary, despite its orientation toward pediatrics. It does not emphasize experimental work but includes some.

(a) This discussion should not be taken as the whole story. There are many factors, environmental and intrinsic, that can modify the response as compared to the standardized laboratory experiment performed at Brookhaven. Also, some of the unicellular plants (e.g., yeasts) do not fit the pattern very well. Further discussion is beyond our scope here.

(b) See chapter 11.

1. Generalizations from the Large-Animal Experiments with Strontium

It is now clear that the ^{90}Sr - ^{90}Y couplet has become a bench mark or reference system for all consideration of bone-seeking beta emitters, much as ^{226}Ra became the bench mark for bone-seeking alpha emitters. The couplet has been studied in a number of different species over very long periods utilizing several different routes of administration.^(a) The large experiments are now essentially complete, and a few generalizations can be made.

- a. There is an important and as yet unexplained qualitative difference between the distribution and effects appearing after oral administration and those after inhalation and most forms of parenteral administration, e.g., intravenous injection. Soft tissue effects, such as hematopoietic dysplasias and myeloproliferative disorders in general, and soft-tissue malignancies in general are much more prevalent after oral administration. Thus, the Hanford experiment with swine and the Davis experiment with dogs show qualitatively different results from the Utah and other experiments where the radionuclide was given by intravenous injection. They were different, too, from the results of inhalation exposure done at Lovelace (Inhalation Toxicology Research Institute). It is true that bone tumors could be produced on all dosage regimens, and some soft-tissue effects could be seen at high doses in nearly all experiments. It was the mix of bone tumors and soft-tissue tumors and other effects referable to soft tissue, including bone marrow, that was so strikingly different. This contrast was first highlighted by McClellan and Jones (1969) in a masterful review prepared for one of the Utah symposia.
- b. Quantitative differences have appeared with different dosage patterns. "In general, exposures that resulted in high-initial dose rates, followed by protracted exposure of localized areas of tissue predisposed to the development of osteogenic sarcoma . . ." (McClellan and Jones 1969, p. 314). The incidence of neoplasms of the hematopoietic system did not show this relation to dosage pattern.
- c. Those experiments that covered more than one generation showed remarkably little effect of a strontium body burden on reproductive performance or on the health of the offspring. Indeed, doses required to produce easily measurable effects on farrowing or on the offspring tended to be definitely toxic to the mother, enough so that parturition was difficult. This generalization seems to have been forgotten in some of the polemics regarding long-term effects of fallout. While it can be argued that long-term studies of the offspring were not sufficient to turn up any subtle genetic or behavioral effects, the above conclusion appears to be based on voluminous and carefully executed experimental work.
- d. The work on strontium contributed enormously to our knowledge of the biochemistry and physiology of bone.

(a) The yttrium component of ^{90}Sr - ^{90}Y equilibrium mixtures is not absorbed from the gut. Therefore, in feeding experiments, the contribution of yttrium comes from that which grows in from the strontium that has been absorbed. In general, when an experiment is stated as having been done with ^{90}Sr , it was usually the ^{90}Sr - ^{90}Y mixture that was given. If injected, the preformed yttrium was included in the effective dose, but if ingested, it was not, except for its dose to the gut wall.

- e. While strontium is clearly able to produce bone tumors, they occur only at quite high levels of radiation dose. There is a very low incidence at the lower levels of radiation dose, even though such levels are well above those associated with fallout from the nuclear weapons tests or normal peacetime operations of the nuclear enterprise. It is very unlikely that the few remaining animals in the large experiments will change this conclusion.^(a) Thus, it is the catastrophic event that poses a real threat from intake of radiostrontium insofar as cancer is concerned.^(b)
- f. Genetic effects of strontium did not receive generous attention, despite the allegations of Sternglass (see chapter 12). The gonadal dose is very small, and in larger animals and man, the gonads are far enough from surrounding bone not to receive a large dose in this manner. The few experimental studies indicate that somatic effects will far outweigh genetic effects of strontium in higher mammals.
- g. The data from the long-term animal experiments have provided the basis for the only complete and tested model for radionuclides in bone, the so-called Marshall model. This used the Norris power function relationship for retention of strontium (see chapters 7 and 8, also Norris and Kisielski 1948) for extrapolation to man. However, there were complications. A large difference in retention time between compact and cancellous bone was apparent. Many preferred a series of exponential functions over the power function as being more physiological and susceptible to future compartmental analysis. The alkaline-earth model as it appears in ICRP Publication 20 (ICRP 1973) recognizes the differences between bone types, but still uses power functions, albeit modified by an exponential. The data are still being reviewed.
- h. The several authors reporting on the long-term experiments concluded that the dose-response relationships were unlikely to be linear to dose.

Tables illustrating the effects of ^{90}Sr (^{90}Y) in the several large animal experiments are given below.^(c) In table 13.18, the bone sarcoma incidence in the Utah dogs as of 1987 is given as part A; bone sarcoma, myeloproliferative disorders, and malignant tumors of soft tissues in the dogs at Davis as part B;^(d) the bone sarcoma, hematopoietic dyscrasias, and soft-tissue tumors in the dogs receiving ^{90}Sr by inhalation at Lovelace as part C.

- (a) A new bone tumor has been found on histological examination of bone from a long-dead Utah dog (Lloyd, personal communication 1987). Thus, the story is not yet complete.
- (b) The long-lived bone-seeking alpha emitters do not show this phenomenon to such a marked degree; the dose-response is more gradual. Effects on other systems were less regularly related to dose.
- (c) Information in this section was extracted from recent tabulations drawn together by a Task Group of the NCRP, chaired by R. D. Lloyd, University of Utah. Contributing members were, P. Durbin, Berkeley; R. Jones, Lovelace; N. J. Parks and R. Pool, Davis; and H. Ragan, PNL. They are brought together here with permission of Dr. Lloyd and with the understanding that they are subject to revision and may or may not represent a consensus of all concerned. The final report is still in preparation. An update to 1987 was supplied by Dr. Lloyd in December 1987.
- (d) The NCRP report will also show results with ^{226}Ra at Davis.

TABLE 13.18. Summary of Dog Experiments with Radiostrontium**A.** Utah—Injection. Bone Sarcoma as of 1987.

Inj. $\mu\text{Ci/kg}$	Avg. yr inj. to death	No. of dogs	Sar.(a) dogs	Incidence (%)	Avg. Skel. rads at death
97.9	3.40	14	8	57.1	10,714
63.6	5.82	12	8	66.7	8,007
32.7	9.98	12	2	16.7	6,282
10.8	12.27	12	1	8.3	2,264
3.46	10.79	12	0	0	628
1.72	11.31	13	0	0	351
0.57	12.93	12	0	0	114
0	11.49	13	0	0	0

(a) Dogs with bone sarcoma.

B. Davis—Ingestion. Beagles given ^{90}Sr at LEHR. Data are as of 30 September 1982. Shown are the number of dogs with bone sarcoma, myelolympho-proliferative syndrome (MPS), and malignant tumors of soft tissues near bone (mainly squamous cell carcinomas of gingiva) for dogs dying or terminated from the experiment.

Group	No. of dogs, dead (alive)	Gp. avg. max. body content μCi/kg	Avg. years to death or term.	Gp. avg. skel. dose, rad	No. of dogs with		
					Bone sar.	MPS	Soft tiss. tum. near bone
Exposed by ingestion							
D00	67 (12)	0	13.6 ± 2.9	0	0	1	0
D05	66 (10)	0.038 ± 0.011	13.0 ± 3.4	31 ± 13	0	0	1
D10	35 (5)	0.097 ± 0.018	12.7 ± 2.5	130 ± 30	1	0	0
D20	61 (3)	0.562 ± 0.090	12.9 ± 3.4	787 ± 210	0	1	0
D30	66 (3)	1.81 ± 0.31	13.1 ± 2.8	2655 ± 650	2	3	7
D40	63	4.99 ± 0.82	10.6 ± 4.0	6053 ± 2134	6 ^(a)	8 ^(b)	12
D50	63	14.5 ± 2.7	5.5 ± 2.7	9810 ± 4117	16 ^(c)	26	10 ^(c)
D60	19	43.1 ± 9.7	2.2 ± 0.5	12750 ± 3810	10	7	1
Exposed by injection ^(d)							
S20	18(1)	3.7	12.8 ± 3.0	765 ± 228	1	1	0
S40	21(1)	9.33	12.5 ± 2.4	6601 ± 1484	6	1	1
					42	48	32

(a) Plus one liposarcoma of bone

(b) Plus one leukemic malignant lymphoma

(c) One of each occurred in the same dog

(d) Five other dogs not included that lived fewer than 500 days after injection.

C. Lovelace (ITRI). Dogs exposed to ^{90}Sr by Inhalation. (Data are as of 30 September 1983, all dogs dead.)

Group	No. of dogs	$\mu\text{Ci/kg}$	Avg. days to death	Avg. skel. dose, rads	No. of dogs with	
					Bone Sarcoma	Tumors of soft tiss. near bone
1	22	0	$4,000 \pm 1,000$	0	0	1
2	25	15	$4,301 \pm 1,240$	$2,076 \pm 760$	1(a)	0
3	14	120	$2,200 \pm 1,010$	$9,300 \pm 1,140$	11	2
4	21	250	$1,780 \pm 930$	$15,000 \pm 2,910$	18(b)	1
					30	4

(a) Plus a disseminated hemangiosarcoma, site of origin undetermined.

(b) Plus two cases of leukemia.

Source: See footnote c, p. 1149.

A general survey of the most commonly observed effects in the three-generation experiment on swine at Hanford is given as table 13.19A and the neoplasia incidence in female swine ingesting ^{90}Sr in table 13.19B. The contrast between ingestion and other routes is highlighted by these summaries.

The results of the work with cats done by the PHS (see section I.F) are not included in tables 13.18 or 13.19 because they were not analyzed by the NCRP group cited above. It was a fairly large program, but perhaps because the project was moved from Cincinnati to Rockville in midstream, so to speak, and because the shorter half-life isotopes of strontium were used, it could not be as long-term as the dog and swine experiments, and it has not received the same continuity of reporting or comprehensive reviews. This work constitutes the only extensive U.S. study of the effects of the shorter half-life strontium isotopes in a species with relatively long life span. The rest of the work with shorter half-life strontium isotopes was done with rodents. The work with cats follows.

Annual reports (DHEW 1966, and sequels) describe the experiment and present results for both metabolism and effects. Two summary reports in 1972 give an overview of the findings (Ward and Wright 1972; Ward et al. 1972). This was well after the EPA had taken over the Twinbrook Laboratory from the PHS.

TABLE 13.19A. Summary of ^{90}Sr Dose Effects in Miniature Swine, Work at Hanford

$\mu\text{Ci/day}$	Observed Effects	Mean Survival Time
625	Pancytopenia-Hemorrhagic crisis, Myeloid Metaplasia	3 months
125	Pancytopenia-Hematopoietic neoplasia, Bone Tumors	3.5 years
25	Neutropenia-Neoplasia	10 years
5	Neutropenia	11 years
1	Neutropenia	11 years

TABLE 13.19B. Neoplasia in Female Miniature Swine Ingesting ^{90}Sr Daily (Percent Incidence). [Work at Hanford. Combined f_1 and f_2 generation, exposure began in utero.]

$\mu\text{Ci/day}$	625	125	25	5	1	0
Mean life span, yr	0.25	3.5	10	11	11	11
Number	24	40	47	29	52	74
Cum. skel.						
Dose, krad	11(a)	14	5	1.5	0.3	0
Bone sar.(a)	8(a)	10				
Myeloid	8(a)	38	9	3		4
Lymphoid		15	9	7	6	1
Liver tum.			23(b)	17	8	8
Intestinal(c)			6		4	1
Ovarian(c)			9			1
Uterine		5	32(d)	48(e)	54(f)	38
Misc.		3	15(g)	3	10	5

(a) Two removed from ^{90}Sr feeding at 3 months of age developed bone tumors and leukemia at 3 and 4 years of ages; remaining animals not removed from ^{90}Sr died at about 3 months of age from bone marrow aplasia.

(b) Two of these tumors were malignant.

(c) All ovarian tumors were malignant.

(d) Four of these tumors were malignant.

(e) Seven of these tumors were malignant.

(f) Four of these tumors were malignant.

(g) Six of these tumors were malignant.

Source: See footnote c, p. 1149.

The route of administration was oral, the feeding period thirty days. Thirty-three cats were involved in the final reports. Bone marrow lesions were extensive and dose-related, and there was hemorrhagic disease with many hemorrhages observed in various organs. At the cellular level, bone marrow cells showed degenerative changes. Neoplasms of both bone and soft tissues adjacent to bone did occur at longer periods (incidence: four lesions in three cats). Thus, this work was consistent with the findings with ^{90}Sr , viz., the oral route shows relatively more soft tissue damage than intravenous or inhalation routes of intake.

As already mentioned, the work with monkeys at Berkeley was very useful for metabolism data, but the doses were not high enough to produce clear-cut biological effects.

These data with large animals tie closely in concept and conclusions to the large experiments with mice described in chapter 8 and also briefly in section II of this chapter.

2. Experimental Work on Man with Strontium

We have already mentioned that work was done with radiostrontium in man by Dr. Herta Spencer and colleagues at the Hines Veterans Administration and the

Montefiore Hospital in New York. This was collaborated on by investigators at HASL and Brookhaven. (See, for example, Spencer, Laszlo, and Brothers 1957; Spencer et al. 1958; Laszlo and Spencer 1959; Spencer et al. 1967, 1972; Spencer, Kramer, and Samachson 1972; and references cited in chapter 19 concerning chelation therapy.) All of this research indicated behavior in man comparable to that found in the animal experiments.

Probably one of the least known semiexperimental studies with radiostrontium in human beings in the United States was done under the auspices of the U.S. Department of Health, Education and Welfare, Bureau of Radiological Health (Kahn et al. 1969). It was a four-year program with infants done largely in the Cincinnati, Ohio, area. It was a metabolic balance study of healthy infants using consecutive twenty-eight-day balance periods. No strontium was given experimentally. There was sufficient radioactivity from fallout, particularly strontium isotopes, to permit reasonably accurate determinations of intake and output and thus metabolism. Metabolic models were designed for calcium and strontium in the infant. They measured stable as well as radiostrontium balance; they produced a detailed picture of gross retention, observed ratios, and accumulation in the body. The data were compared to models for the very young developed from animal experiments by the people at Utah and elsewhere.

Much work on whole-body retention of the alkaline-earths in man was done abroad and has been cited in part elsewhere.

In chapter 6, we mentioned Hamilton's early idea that radiostrontium might become a therapeutic tool. Little was done on effects in man after that work was discontinued. The only study that looked seriously for effects in man came not from an interest in fallout but from work with luminizers in Czechoslovakia, which was described briefly in chapter 1. Müller and colleagues (1961) measured urinary excretion of strontium-yttrium in many workers and found signs of hematological changes. This was followed up by a large study described in a monograph from the Institute of Radiation Hygiene in Prague (Müller and coworkers 1970). The body burdens estimated from urinary excretion were confirmed by whole-body counting. Karyological examinations of circulating peripheral lymphocytes were considered worthy of consideration as a biological dosimeter, but no clearly deleterious effects were found.

B. Iodine

There were no extensive animal experiments with radioiodine generated by the problems of fallout that we have not already reviewed at least in part. The Hanford symposium on iodine, held in 1963 and discussed in some detail in chapter 8, was exceptionally complete, partly because the work got an early start around the site-specific problems. The really new information has come from the environment itself and clinical medicine.

It was around iodine that the importance of the food chain was highlighted, particularly the role of the contamination of milk, which led to drastic reduction of permissible releases, as we have seen. Also, the environmental work led to de-emphasis of the importance of the inhalation pathway for iodine. The chief contributions of experimental research to these matters were to confirm and strengthen, under controlled conditions, the conclusions already reached on the basis of environmental investigations.

The above is not to imply that experimental work with iodine came to a standstill. It did not, but its orientation was more general than fallout problems

alone. One of the key questions through many years of new experimental work is one that has as much bearing on nuclear medicine and clinical aspects of iodine as on fallout problems. This is the question as to whether or not the different isotopes of iodine, with their very different half-lives and thus different specific activities, have different degrees of effectiveness. Also, are they different from a comparable absorbed dose of external radiation? Evidence began to accumulate that there was a difference. The longer-lived iodines like ^{131}I seemed to be less effective than comparable absorbed doses from external radiation or short-lived iodines. This came largely from animal experiments and clinical observations. It stimulated more experiments.

A tabular summary of much of the pertinent experimental work is shown as table 13.20, which was modified from the work of another task group of the NCRP, whose report has recently been published (NCRP Report No. 80 [NCRP 1985]). The group was chaired by Dr. Harry Maxon, University of Cincinnati. Members are S. R. Thomas and C. R. Bunker, University of Cincinnati; D. V. Becker, New York Hospital; S. A. Book, University of California at Davis; and E. L. Saenger, University of Cincinnati as advisor.

TABLE 13.20. Summary of Experimental Animal Studies on the Effectiveness of ^{131}I Relative to X-Irradiation or to Short-Lived Radioiodines

Author (date)	Species	Effect	Dose or Dosage			Effectiveness of I-131(a)
			X-ray	I-131	Other	
Tumorigenesis						
Doniach (1957)	Rat	Thyroid adenomas, cancers	1,100 rads	30 μCi , est. by Doniach to give 2,000- 24,000 rads		1/2-1/20
Lindsay et al. (1957)	Rat	Thyroid adenomas, cancers	1,000 R	25 μCi 5,000 rads (estimated by Book)		1/5
Lindsay et al. (1961)	Rat	Thyroid adenomas, cancers	1,000 R	25 μCi 5,000 rads (estimated by Book)		1/5
Walinder (1972)	Mouse	Thyroid adenomas, cancers	1,500 R	6,400-16,000 rads		1/4-1/11
		Thyroid adenomas, cancers	1,000 R	2,200-11,000 rads		1/2-1/11
Lee et al. (1982)	Rat	Thyroid adenomas, 1,060 carcinomas	94- 1,060 rads	80-850 rads		1/1-1/2.5 for adenomas 1/1 for carcinomas

TABLE 13.20. Continued.

Author (date)	Species	Effect	Dose or Dosage			Effectiveness of I-131(a)
			X-ray	I-131	Other	
Other Effects						
McClellan et al. (1963)	Sheep	Histologic changes	750- 3,000 R	24,000- 90,000 rads		1/20
Greig et al. (1970)	Rat	Inhibition of goitro- genesis	100- 1,800 rads	530- 51,000 rads		1/5 at low doses; 1/15- 1/30 at high doses
Klassovskii et al. (1970)	Rats and Dogs	Histologic, functional changes		Hundreds to tens of thousands of rads from I-131 or mixture of 10% I-131 and about 90% I-132, I-133, I-135		1/10-1/25
Walinder & Sjoden (1971)	Mouse	Inhibition of goitro- genesis	1,500 rads	1,000- 14,000 rads		1/2-1/4
Walinder, Johnson, & Sjoden (1972)	Mouse	Thyroid gland growth	180 rads	1,500- 2,000 rads		1/5-1/10
Walinder et al. (1972)	Mouse	Inhibition of goitro- genesis	1,000- 1,500 rads	4,000- 5,000 rads	1,200- 2,400 rads from I-132	not stated but suggests X-ray and I-132 about the same
Book et al. (1980)	Rat	Inhibition of goitro- genesis		60- 16,000 rads	1-800 rads from I-132	1/9

(a) Relative to X-ray or other radioiodine isotopes.

Source: Modified from NCRP report 1985. The cited references have been placed in the bibliography for this chapter. NCRP Task Group chaired by H. Maxon.

Obviously, there appear to be differences in effectiveness between ^{131}I and external radiation or shorter half-life iodines, with ^{131}I frequently but not always less effective. The range of differences is quite large, and decisions regarding a single figure to use for radiation protection purposes are difficult. The same type of difference has appeared in clinical studies. Saenger et al. (1963) reviewed these as early as the Hanford symposium on iodine; they have been confirmed qualitatively ever since.

This phenomenon came to light because important clinical problems stimulated investigation. Other instances where different isotopes of important

elements have different effectiveness are discussed at various points in this book, (e.g., ^{238}Pu versus ^{239}Pu).

However, there has not been a systematic investigation of the presence or causation of these phenomena throughout the internal emitter field. Thus, for estimates of risk, we frequently can only assume that a given absorbed dose from an internally deposited radionuclide will be roughly equivalent to the same dose from an external source. This may or may not be a safe generalization and is a fitting subject for future research.

As for mechanisms, in the case of iodine, dose rate and relative binding to colloid in the thyroid have been considered. In the case of ^{238}Pu versus ^{239}Pu , relative in-situ radiolysis has been considered. We need a more generalized set of explanations and investigations of the phenomena in terms of both occurrence and mechanisms.

C. Cesium

Obviously, this radionuclide received much attention in both laboratory and field. There was not as much overt organization of experimental work around it as around the bone seekers. There are few large compendia devoted to cesium compared to those for strontium, radium, plutonium, et al. We will give a very condensed overview of what was done, knowing that much of it has already been discussed.

1. Consideration of Animal Experiments

There were a few major animal experiments on ^{137}Cs . One began during the peak of research activity around fallout. This was an experiment at ANL in which about seventy dogs in three age groups were given ^{137}Cs intravenously. The doses were large: 1,650 to 4,310 $\mu\text{Ci } ^{137}\text{Cs/kg}$, and it was a lifetime study. A good review of what occurred can be found in an NCRP report on cesium prepared by its former Committee-23 on Radiation Hazards Resulting from the Release of Radionuclides into the Environment (NCRP 1977). The last animals had died just before the report was prepared, and the Argonne workers supplied the NCRP Committee with the final figures.^(a) There were also useful status reports in the ANL annual reports (e.g., Poole, Norris, and Fritz 1968).

Bone marrow destruction was a leading cause of death, but there were many other changes in soft tissue that led to fatal consequences. There was higher acute toxicity in older dogs associated probably with the increasing half-time of ^{137}Cs with age demonstrated by Tyler, Kretz, and Norris (1969). The distribution of dose was found to be clearly much more generalized than with an element like strontium. Indeed, cesium exposure is much like whole-body exposure with external radiation. In the ANL experiment, accumulated average total body dose to forty dogs surviving the acute phase was 1,170 rad (696 to 1,643 rad), with an average survival time of 3,590 days (2,010 to 5,099 days). Significant degeneration of the liver occurred in nearly all of the long-term survivors.

A somewhat later but basically similar experiment was performed at the Lovelace Foundation. There were over fifty beagles, all thirteen months of age. They

(a) The Committee was chaired by John C. Brugher until his death in 1970 and then by Walter S. Snyder. Members were Seymour Abrahamson, H. L. Andrews, C. L. Comar, G. B. Forbes, P. F. Gustafson, J. H. Marshall, C. W. Mays, and J. Rivera.

received intravenous injections of from 880 to 4,000 $\mu\text{Ci } ^{137}\text{Cs/kg}$, and the individual total body doses ranged from 550 to 2,200 rad. Bone marrow destruction was again a prominent finding, but there were many other changes, including carcinoma of various soft tissues. The total body dose required to kill 50% of the animals in this experiment was about 1,000 rad.

The total doses involved when serious effects occurred in these experiments should be compared with the much higher doses associated with bone tumors produced by strontium isotopes (tables 13.18 and 13.19). Even though some of the difference resides in the dosimetry, especially a highly localized dose versus a whole-body dose, the differences are notable. While the ^{137}Cs doses seemed high to the investigators, and indeed they are higher than the LD_{50} dose of external radiation, they are sufficiently lower than those with radiostrontium to raise questions regarding the single-minded worries about strontium in fallout and in the environment. The authors of the NCRP report are quick to point out that the effects per rad at low doses may be quite different from those observed in long-term survivors of an acute lethality experiment.^(a) This may well be true. Yet, this author views the dose from cesium associated with such marked damage as worthy of note in evaluating the long-term effects of fallout. It is true that the half-life of cesium is much shorter than that of ^{90}Sr , and it is traditional to worry most about the elements that remain in the environment for a long time, a factor that may be enough to support focusing attention on strontium. Yet, as we have gradually learned about long-term sequelae of high radiation doses given promptly, the potential for such sequelae from cesium should be earmarked for future work.^(b)

The Lovelace group included ^{137}Cs in the extensive inhalation studies described in detail in chapter 9. The soluble forms, e.g., $^{137}\text{CsCl}$, gave essentially whole-body doses and produced bone marrow aplasia by one year, as well as some neoplasia of various organs at later times. Insoluble forms, such as those in which the element is fused into aluminosilicate clay particles, were studied extensively with elements like ^{90}Sr , ^{90}Y , and ^{144}Ce but were not used much for cesium. However, there is no reason to expect that ^{137}Cs in such a form would behave very differently. In general, of course, these insoluble forms deliver large doses to lung and the respiratory tract and do not simulate a whole-body exposure. In a field exposure to fallout, it seems likely that inhalation exposures would involve a preponderance of insoluble material and thus be of less significance than soluble forms entering food chains. The bulk of the dose from ^{137}Cs in fallout could thus be via food chains, except in acute accidents. As we have already seen, cesium is very mobile in many environmental situations, especially when fresh, and it finds its way into milk and other foodstuffs with ease.

2. Experimental Work with Humans

Metabolic studies on ^{137}Cs were carried out in the metabolism ward by Herta Spencer and collaborators (Rosoff, Cohn, and Spencer 1963) much as was done for strontium. In this work, the patients had disease entities that confined them to the hospital, but their sickness was not expected to interfere with the metabolism of cesium. Tracer doses were given intravenously to four patients and

(a) No major experiment appears to have been done at really low doses of cesium, such as those that might be associated with global fallout from weapons tests.

(b) Environmental recycling of cesium adds to this concern.

orally to seven. As expected from animal experiments, the cesium was rapidly absorbed and rapidly excreted, largely via the kidneys. Nevertheless, body retention, determined from excretion data, was on the order of fifty to sixty days (retention half-time). Thus, cesium does bind to tissues and/or there is exchange and replenishment. Incidentally, there appeared to be significant binding of cesium to red blood cells (mechanism not discussed). This is reminiscent of the behavior of ^{210}Po as described in chapter 4. Tissue distribution was relatively uniform in soft tissues by ten days after intake and thereafter.

A follow-up report (Cohn et al. 1963b) described the retention of ^{137}Cs in man for extended periods using the whole-body counter at Brookhaven. The subjects were patients, two receiving intravenous doses and three receiving oral doses. Considering only the final long-term exponential component of the retention curve, values of biological half-life ranged from 54 to 114 days, with a mean of 75 days. This was within the error range of the values obtained from excretion analyses. Again they indicate that the body is not a sieve for cesium.

The experimental study by Cohn et al. lasted 343 days. A study of cesium retention in man by Richmond, Furchner, and Langham (1962), also Richmond, London, and Furchner (1964), went for 550 days in one subject and 940 days in another. (This was not experimentally administered cesium, but that accumulated from fallout.) The biological half-life was not markedly different from that in experimental studies.

These research efforts tie well qualitatively to the conclusions described earlier from site-specific and fallout data and animal experiments, including the general views found in the UNSCEAR and FRC reports.

D. Cerium

We have not placed or seen much emphasis on radiocerium per se in this book. However, it is a member of the important lanthanon series, and we have had things to say about these. The isotopes of most interest to humans are ^{141}Ce , ^{143}Ce , and ^{144}Ce . We saw much of ^{144}Ce in the inhalation experiments of the Lovelace Foundation (chapter 9) and as a component of fallout (chapter 12).

Large quantities of radiocerium are produced and released to the atmosphere in nuclear weapons testing. While not studied intensively, it has not been neglected entirely for experimental work. When a committee of the NCRP set about reviewing the findings on a number of radioelements, a very respectable volume of material on radiocerium was found to be available. It was reviewed by NCRP Committee-30, and a report was published in 1978 (NCRP 1978).^(a) The objective was examination of data particularly pertinent to radiation protection.

Concentration factors from soil to plant for ^{144}Ce are low in fish (table 11, NCRP 1978) and gastrointestinal absorption is low. However, concentration factors in aquatic foodstuffs average from one in laboratory animals (table 10, NCRP 1978) to as high as two thousand (maximum) in some mollusks. Factors against freshwater can go as high as 10,000 for some plant species. Much work

(a) The Committee was chaired by R. O. McClellan, Lovelace, and members were: J. E. Ballou, PNL; R. G. Cuddihy, Lovelace; P. W. Durbin, Berkeley; M. Goldman, Davis; M. J. (Cook) Hilyer, Oak Ridge; B. Kahn, Georgia Tech; F. W. Lengemann, Cornell; A. Lindenbaum, ANL; Y. Ng, LLL; C. R. Richmond, Oak Ridge; J. S. Robertson, Mayo Clinic; B. O. Stuart, Stauffer Chemical Company; and R. G. Thomas, Los Alamos.

has been done on the metabolism of inhaled radiocerium. Inhalation of the soluble chloride led to significant concentrations in liver and skeleton and rapid removal from the lung, whereas inhalation of an insoluble form resulted in a larger fractional dose to the lung. Several species of animals have been used (table 14, NCRP 1978). After injection, there was more ^{144}Ce in liver than in skeleton, but in small rodents it tended to leave rapidly.

Effects of cerium after inhalation have been extensively studied in the United States. An illustration of the survival and current status of beagle dogs receiving ^{144}Ce as fused aluminosilicate particles (FAP) is given as figure 13.21A. Similar information for soluble ^{144}Ce chloride is shown in figure 13.21B. Obviously, there is a different mix of effects from the inhaled soluble compared to the insoluble forms of the same element. Note also the calculated doses at which marked effects begin to occur.

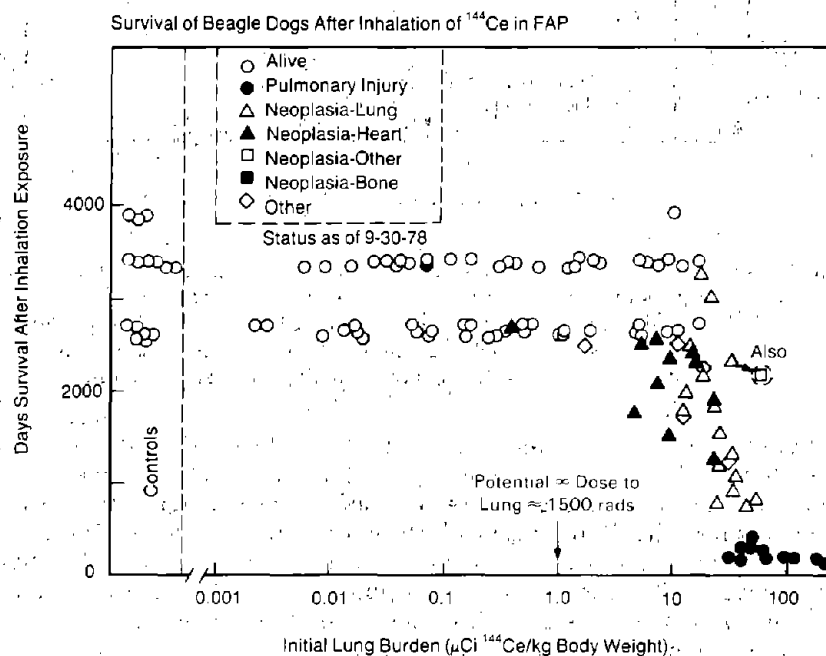


FIGURE 13.21A. Dose-response relationship for the effect of ^{144}Ce on the lung and other organs of beagles after inhalation of labeled fused aluminosilicate particles (as of September 1978). (Redrawn from NCRP 1978, p. 59. Reprinted with permission of the NCRP, Bethesda, Maryland, copyright 1978.) Experimental work done at Inhalation Toxicology Research Institute.

There was some work with radiocerium using intravenous and intraperitoneal routes of administration. Some of it employed beagles, but much of it was with rodents. Much of the latter was done in the USSR. In all of these, marked damage to bone marrow, liver, and gastrointestinal tract occurred; yet, changes also appeared in lung and in skeleton, including osteosarcomas. Thus, cerium may

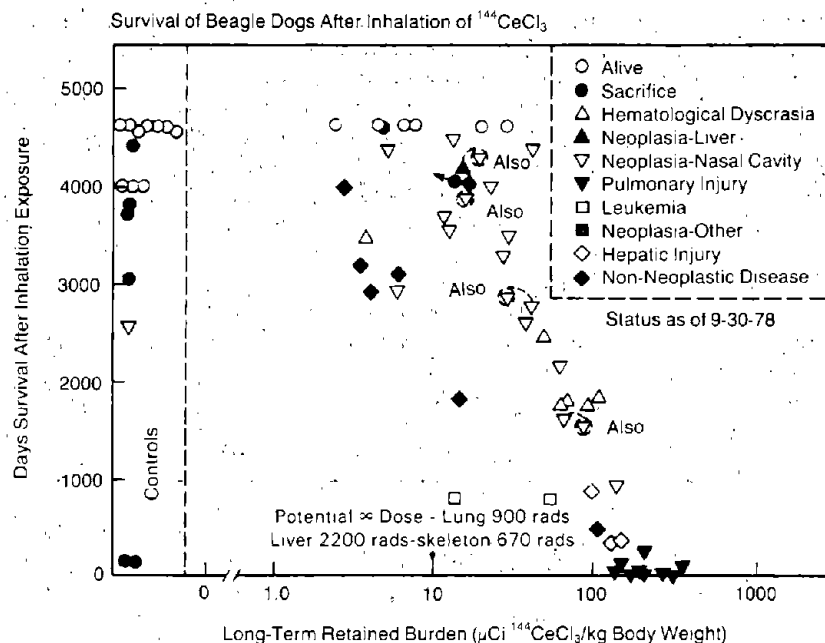


FIGURE 13.21B. Dose-response relationship for the effect of ^{144}Ce on the lung and other organs of beagles after inhalation of ^{144}Ce labeled chloride aerosols (as of September 1978). (Redrawn from NCRP 1978, p. 67. Reprinted with permission of the NCRP, Bethesda, Maryland, copyright 1978.) Experimental work done at Inhalation Toxicology Research Institute.

stand between the bone seekers and radionuclides like cesium that essentially irradiate the whole body. Bone tumors cannot be excluded as a late effect with cerium. This contrasts to cesium. Yet the soft-tissue damage from cerium is more generalized than is the case with strontium, on the average. Current data do not allow direct estimates of risk of the several types of effects. It is hoped that future work will make such estimates possible. Until we have a true picture of comparative risk, we are probably likely to unintentionally over- or under-emphasize one type of effect compared to another.

E. Other Radionuclides

The enormous enterprises with tritium and the actinides have been amply discussed elsewhere in this book. We need only remember that tritium may sometimes be underemphasized in biological significance because of its generally low toxicity. The actinides, by contrast, have retained their reputation, developed very early, as highly toxic and especially potent carcinogens. There are no additional biomedical data that need summarizing here. In comparison to fission products, the actinides are not of concern in the early periods of fallout. It is in the long pull from both fallout and in waste disposal that their possible health effects become most important. There were some special environmental problems with plutonium, in particular, which we will need to review in the next chapter.

V. Summary and Commentary

The scare thrown into the biomedical community, as well as society in general, by the problems of fallout from nuclear weapons tests stimulated much expansion of research on the radionuclides in fallout. Some of it was primarily an expansion of the work on fission products described in chapters 6 and 8. Some of it could be regarded as essentially new. All of it was correlated with knowledge and ideas that were already appreciated but in need of very significant expansion. In all cases, the resources and personnel thrown into the effort were far above anything that would have occurred without the fallout scare.

At least seven new laboratories came into being, in part, at least, to attack various aspects of these problems by experimental means. The earliest was the Naval Radiological Defense Laboratory at San Francisco. This originated around the problems first appreciated at Operation Crossroads (chapter 12). Much of their work was very practical, but they also engaged in rather basic biomedical research, including aquatic biology. In fact, the laboratory became a center for several types of radiobiological work, developed a sizeable animal colony and research staff, and was very well equipped by the time of its closing in 1969.

The cattle with beta burns on their backs from the Trinity shot were the progenitor for a very considerable research effort at Oak Ridge. The organization was separate from the Oak Ridge National Laboratory. It was a cooperative effort between the AEC and the University of Tennessee Agriculture School. It was called the UT-AEC Farm and was the site of much laboratory research with strontium, iodine, and other fallout radionuclides. It was here that Cyril Comar and his colleagues worked out the so-called "observed ratio" (OR) approach for comparison of the metabolism of strontium with that of calcium and for other pairs of elements in plant and animal systems. The laboratory was later renamed the "Comparative Animal Research Laboratory" and the work proceeded without the single-minded devotion to fallout problems it had during its prime years. Much of what we learned about the discrimination between elements normally present in significant quantities in living organisms and their homologues was generated by work at the UT-AEC Farm and at Cornell University, where Dr. Comar transferred in 1957, as well as in work at Hanford.

The Laboratory of Physical Biology at the New York State College of Veterinary Medicine at Cornell University carried forward and expanded work on mineral metabolism of the type begun by Comar and his staff at the UT-AEC Farm. Both laboratories specialized in the use of large animals and devoted much attention to transfer into milk, across the placenta, the movement of radionuclides through food chains, and to fundamental radiobiology.

The fourth new laboratory developed around the problems of fallout was at the University of California at Davis. Its organization was described in chapter 8, but the results of its long-term feeding of strontium to beagles and of injected radium are described briefly in this chapter. There was little doubt that the distribution of effects in the beagle was not the same on a feeding regimen as after intravenous injection.

At least two major laboratories were developed anew by the U.S. Public Health Service in response to the problems of fallout. The first was the Southwestern Regional Radiological Health Laboratory in Las Vegas. This was a diversified program with laboratory work at Las Vegas and a field station for large animals and controlled ecological studies at the Nevada Test Site. It included work with fistulated steers, agronomy, and a major effort at methods for removing strontium from milk. All of this was in addition to their work in offsite

environmental monitoring described in chapter 12. In 1970, the laboratory came under the Environmental Protection Agency, and its program has gradually broadened to include nonradioactive contaminants of the environment.

At the Robert A. Taft Center of the Public Health Service in Cincinnati, a breeding colony for cats was established, and the metabolism and effects of strontium and iodine in the feline were studied. There were some contrasts with other species. There was also experimental work on freshwater biota. After a few years, this program was transferred to the Twinbrook facility in Rockville, Maryland.

Among the last of the new laboratories developed in the period we are reviewing were the Biomedical Program at the Lawrence Livermore Laboratory and the inhalation program at the Lovelace Foundation. The latter was directed to the metabolism and effects of inhaled fission products. However, fallout problems were not predominant in its genesis since there are greater potential inhalation problems from reactor fission products. Its work and results are described in chapter 9. By contrast, the program at Lawrence Livermore was originally centered on fallout problems, with special reference to Project Plowshare. This will be reviewed primarily in chapter 14, but was touched upon in chapter 12.

In addition to laboratories developed *de novo*, many of the established laboratories modified and expanded greatly their programs in areas related to the problems of fallout.

Some of the largest and longest experiments on the metabolism and effects of fallout radionuclides were developed at Hanford (later Battelle, Pacific Northwest Laboratories). There was a multigenerational study of strontium in miniature swine; studies of fallout radionuclides in adult, fetal, and juvenile mammals; and the transfer of pairs of elements in plants. This last produced results somewhat at variance with the OR approach used by Comar. All of this was in addition to the multigenerational experiment with iodine that was already under way before the fallout problems became pressing.

The continuation and expansion of the comparative toxicity experiment with mice at Argonne National Laboratory (chapter 8) could be considered, in part, a research response to the problems of fallout. At least the results became part of the fallout controversy as described in this chapter.

Brookhaven made contributions to the research needs of the fallout days by definitive work on mineral metabolism, especially using the whole-body counter. Much of the work involved man rather than animals. There was also a significant program involving plants.

The University of California at Berkeley, the seat of the original research on fission products, added a study of strontium metabolism in the rhesus monkey and later on actinides in the cynomolgus monkey. The latter is now reaching fruition.

Additions to the research programs also occurred at Rochester and Los Alamos, plus a unique mixture of field and glasshouse studies on plants and plant-soil interactions at the University of California at Los Angeles. In this case, the field studies were at the Nevada Test Site, the experimental work at the University.

The results of the new and of the expanded research efforts are described in the chapter, plus some generalizations on how the many experiments described in chapter 8 meshed with them. There is no doubt that we now have considerable information, perhaps more than for any of the common chemically toxic

pollutants, even lead, mercury, and cadmium as a result of research stimulated by the problems of fallout. The principal area of doubt concerns the risks of very low-level, long-term intakes of the fallout radionuclides just as in the case of external radiation. Also, it seems clear that strontium is becoming a benchmark for the beta emitters as radium became for the alpha emitters, except that all of the evidence for effects of strontium has been obtained from animal experiments rather than from human experience, for which we can be thankful.

Note 1(a)

Selected reports and publications in the biomedical area from the NRDL, San Francisco, California, especially pertinent to assessment and research on problems of fallout. Emphasis is placed on NRDL reports. Many publications are cited elsewhere in this and other chapters.

- Sondhaus, C. A. 1952. *The ratio of lung beta dose to whole-body dose during given time intervals after an atomic bomb detonation*. USNRDL-394, dated December 31, 1952, declassified May 16, 1957.
- Cohn, S. H. and J. K. Gong. 1953. Effect of chemical agents on the skeletal content and excretion of injected strontium-89. *Proc. Soc. Exp. Biol. Med.* 83:550.
- Cohn, S. H. and J. K. Gong. 1953. Effect of 200 roentgens local x-irradiation on the metabolism and alkaline phosphatase activity of rat bone. *Am. J. Physiol.* 173:115.
- Cohn, S. H. and J. K. Gong. 1953. *Effect of 500 roentgens whole-body x-irradiation on the growth and metabolism of rat bone*. USNRDL-381.
- Cohn, S. H. and J. K. Gong. 1953. Effect of 2000 roentgens local x-irradiation on the growth of rat bone. *Growth* 17:7.
- Cohn, S. H., J. K. Gong, and M. C. Fishler. 1953. EDTA treatment of internal radioactive contamination. *Nucleonics* 11:56.
- Bunney, L. R. and H. E. Ballou. 1954. *An estimate of the predominant chemical species resulting from a shallow underwater burst of an atomic bomb*. USNRDL-435.
- Gong, J. K., W. L. Milne, and S. H. Cohn. 1954. *Studies on the treatment of internal radioactive contamination. IV. Effect of zirconium citrate and EDTA on the distribution and excretion of a mixture of long-lived fission products*. USNRDL-426 and *Fed. Proc.* 13:312.
- Greendale, A. E. and N. E. Ballou. 1954. *Physical state of fission product elements following their vaporization in distilled water and seawater*. USNRDL-436.
- Cohn, S. H. and others. 1955. *Uptake, distribution, and retention of fission products in tissues of mice exposed to a simulant of fallout from nuclear detonation*. Project NM-006-011.04.
- Cohn, S. H., R. W. Rinehart, J. K. Gong, J. S. Robertson, W. L. Milne, and V. P. Bond. 1955. *Nature and extent of the internal radioactive contamination of human beings and animals exposed to fallout material in Operation Castle*. USNRDL-TR-86.
- Cronkite, E. P. et al. 1955. Study of responses of human beings exposed to significant fallout radiation. *J. Am. Med. Assoc.* 159:430.

- (a) This is but a small sample of NRDL reports and publications (listed chronologically). The entries are chosen to illustrate facets of the work not likely to be generally known. Numerous formal and progress reports exist, many of them on very practical problems of contamination and decontamination. Much of it is in the hands of the Navy Historian and in the Hearings of the Joint Committee on Atomic Energy of the U.S. Congress, cited in chapter 12.

- Rinehart, R. W., S. H. Cohn, J. Seiler, W. Shipman, and J. K. Gong. 1955. *Residual contamination of plants, animals, soil and water of the Marshall Islands one year following Operation Castle fallout*. USNRDL-454.
- Bolles, R. C. and H. E. Ballou. 1956. *Calculated activities of U-235 fission products*. USNRDL-456.
- Cohn, S. H. 1956. *Radiation and the individual in the atomic age*. USNRDL-RL-23.
- Cohn, S. H., J. K. Gong, and W. L. Milne. 1956. Ability of chemical agents to alter the uptake and retention of fission products in animals exposed to radioactive fallout. Presented at a meeting on "Experimental and chemical approaches to treatment of poisoning with radioactive substances," held at Argonne National Laboratory, October 1955. *Arch. Ind. Health* 14:533.
- Cohn, S. H., W. R. Lane, J. K. Gong, and W. L. Milne. 1956. *Radiotoxicity resulting from exposure to fallout simulant: The metabolism of inhaled and ingested simulant of fallout produced by land-based nuclear detonation*. USNRDL-TR-118.
- Cohn, S. H., W. R. Lane, J. K. Gong, J. Sherwin, and W. L. Milne. 1956. Uptake, distribution and retention of fission products in the tissues of mice exposed to a simulant of fallout from nuclear detonation, 1. Simulant of fallout from detonation under sea water. USNRDL-TR-77. *Arch. Ind. Health* 14:333.
- Cohn, S. H. and W. L. Milne. 1956. *Effects of combined administration of Sr⁹⁰ and external radiation*. USNRDL-TR-89.
- Cohn, S. H., R. W. Rinehart, J. K. Gong, J. S. Robertson, W. L. Milne, W. H. Chapman, and V. P. Bond. 1956. *Internal deposition of radionuclides in human beings and animals: A report on the Marshallese and Americans accidentally exposed to radiation from fallout and a discussion of radiation injury in human beings*, eds. E. P. Cronkite, V. P. Bond, and C. L. Dunham, chapter 6. AECD-TID 5358. Washington, D.C.: U.S. Government Printing Office.
- Cohn, S. H. and others, USNRDL and U.S. Naval Medical Research Institute. 1956. *Internal radioactive contamination of human beings accidentally exposed to radioactive fallout material*. USNRDL-TR-86. Bethesda, Md.
- Farma, P. 1956. *Study of airborne activity resulting from decontamination of ships contaminated with radioactive fallout*. Project NS 083-001.
- Weiss, H., S. H. Cohn, W. Shipman, and J. K. Gong. 1956. *Residual contamination of plants, animals, soil and water of the Marshall Island two years following Operation Castle fallout*. USNRDL-455.
- Cohn, S. H., W. B. Lane, J. K. Gong, L. Weisbecker, and W. L. Milne. 1957. *Studies on the metabolism of inhaled aerosols of strontium and lanthanum*. USNRDL-TR-175. Also *Radiat. Res.* 1:308 (abstr.).
- Cohn, S. H. et al. 1957. The preparation and biological application of airborne simulants of fallout from nuclear detonation: An experimental approach for the estimation of the inhalation hazard following exposure to radioactive fallout. Presented at the American Chemical Society air pollution symposium, held September 15, 1956. *J. Air Pollut. Control Assoc.* 7:30.
- Gong, J. K., W. H. Shipman, H. V. Weiss, and S. H. Cohn. 1957. Uptake of fission products and neutron-induced radionuclides by the clam. *Proc. Soc. Exp. Biol. Med.* 95:3.
- Williamson, W., Jr. 1957. *Investigation and correlation of some physical parameters of fallout material*. USNRDL-TR-152.
- Cohn, S. H., J. K. Arnold, and W. L. Milne. 1958. Effect of whole body x-irradiation on the accretion and exchange of radiostromium in the skeleton on the dog. USNRDL-TR-219. *Fed. Proc.* 13:1.
- Leahy, E. J. and A. L. Smith. 1958. *Contamination control procedures for special weapon accidents*. USNRDL-TR-283.
- Schwab, C. R. 1958. *Radiological safety in special weapons accidents*. USNRDL-TR-273.
- Cohn, S. H. 1959. *Hazards from inhaled radioactive fallout. Biological and environmental effects of nuclear war*. Hearings before the Joint Committee on Atomic Energy, 86th Cong., 1st Sess. Special subcommittee on radiation, pt. I, pp. 482-96. Washington, D.C.: U.S. Government Printing Office.

- Robertson, J. S. and S. H. Cohn. 1959. Radiotoxicity of internally-deposited radioactive material. In *Atomic Medicine*, ed. Behrens. Baltimore, Md.: Williams and Wilkins.
- Cohn, S. H., J. S. Robertson, and R. A. Conard. 1960. Radioisotopes and environmental circumstances: The internal radioactive contamination of a Pacific Island community exposed to local fallout. In *Radioisotopes in the biosphere*. Minneapolis, Minn.: Univ. of Minn. Press.
- Conard, R. A., S. H. Cohn, et al. 1960. Medical status of Marshall Islanders in 1959, five years after exposure to fallout radiation. *Nucl. Med.* 1:314.
- Cohn, S. H., W. B. Lane, J. K. Gong, R. K. Fuller, and W. L. Milne. 1961. Metabolism of an inhaled and ingested simulant of fallout produced by a land-based nuclear detonation. In *Proceedings of an international symposium on inhaled particles and vapours*, ed. C. N. Davies, pp. 178-90. Oxford: Pergamon Press.
- Sulist, R. A., E. J. Leahy, and A. L. Balette. 1961. *Principles of radiation and contamination control*. NAVSHIPS 250-341-3. vol. 3, p. 147.
- Schuert, E. A. undated. *A fallout plotting device*. USNRDL-TR-127.
- USNRDL Technical Program Summary. 1968. Listings of work sponsored by Bureau of Medicine and Surgery of Navy Department and directed by E. Alpen and G. Leong include: Radiation effects on cellular regulation; Biochemical basis of radiation sensitivity; Ontogenesis of the immune response; Partial body radiation; Biological effects of shielding; Radiation effects on gastrointestinal function; Therapeutics and modification of radiation injury in mammals by biological and chemical means; Hazards of airborne radioactive materials; Alteration of physiological functions following exposure to ionizing radiation; Biological effects of microwave radiations. [Under "other support," we find work on high energy neutron irradiating transport of fission products of marine organisms, beta doses from fallout particles, and others.]

Note 2(a)

Selected publications from the UT-AEC Farm. Items listed (in chronological order) are mostly in addition to work already referenced in the text.

- Comar, C. L., S. L. Hansard, S. L. Hood, M. P. Plumlee, and B. F. Barrentine. 1951. Use of calcium-45 in biological studies. *Nucleonics* 8:19-31.
- Hansard, S. L. 1951. Radioisotope procedures with farm animals. 1. Metabolism facilities. *Nucleonics* 9:13-25.
- Hansard, S. L., C. L. Comar, and M. P. Plumlee. 1951. Effect of calcium status, mass of calcium administered and age on Ca^{45} metabolism in the rat. *Proc. Soc. Exp. Biol. Med.* 78:455-60.
- Hansard, S. L., M. P. Plumlee, C. S. Hobbs, and C. L. Comar. 1951. The design and operation of metabolism units for nutritional studies with swine. *J. Anim. Sci.* 10:88-96.
- Harris, H. C., W. H. MacIntire, C. L. Comar, W. M. Shaw, S. H. Winterberg, and S. L. Hood. 1951. Radioactive calcium in the study of additive and native supplies in the soil. *Science* 113:328-29.
- Comar, C. L. 1952. Skeletal metabolism studies with radiocalcium. In *The role of atomic energy in agricultural research*, TID-5115, pp. 225-39. Paper presented at the 4th annual Oak Ridge summer symposium.
- Hansard, S. L., C. L. Comar and M. P. Plumlee. 1952. Absorption and tissue distribution of radiocalcium in cattle. *J. Anim. Sci.* 11:524-35.
- Harris, H. C., W. H. MacIntire, C. L. Comar, W. M. Shaw, S. H. Winterberg, and S. L. Hood. 1952. Use of Ca^{45} labeled calcium carbonate in determining proportions of native and additive calcium in lysimeter leachings and in plant uptake. *Soil Sci.* 73:289-98.

(a) University of Tennessee-U.S. Atomic Energy Commission installation at Oak Ridge, Tennessee.

- Plumlee, M. P., S. L. Hansard, C. L. Comar, and W. M. Beeson. 1952. Placental transfer and deposition of labeled calcium in the developing bovine fetus. *Am. J. Physiol.* 171:678-86.
- Hansard, S. L. 1953. A metabolism unit designed for radioisotope balance studies with dogs. *Science* 117:301-2.
- Hood, S. L. and C. L. Comar. 1953. Metabolism of cesium-137 in rats and farm animals. *Arch. Biochem. Biophys.* 45:423-33.
- Kulwich, R., S. L. Hansard, C. L. Comar, and G. K. Davis. 1953. Copper, molybdenum and zinc interrelationships in rats and swine. *Proc. Soc. Exp. Biol. Med.* 84:487-91.
- Rust, J. H., J. L. Wilding, B. F. Trum, C. S. Simons, A. W. Kimball, and C. L. Comar. 1953. The lethal dose of whole-body tantalum¹⁸² gamma irradiation for the burro (*Equus Asinus Asinus*). *Radiology* 60:579-82.
- Visek, W. J., R. A. Monroe, E. W. Swanson, and C. L. Comar. 1953. Calcium metabolism in dairy cows as studied with Ca⁴⁵. *J. Dairy Sci.* 36:373-84.
- Belanger, L. F., W. E. Lotz, W. J. Visek, and C. L. Comar. 1954. Autoradiographic visualization with Ca⁴⁵ of normal growth of the incisor of pigs and the effects of fluorine feeding. *Anat. Record* 119:53-70.
- Feaster, J. P., S. L. Hansard, J. T. McCall, F. H. Skipper, and G. K. Davis. 1954. Absorption and tissue distribution of radiözinc in steers fed high-zinc rations. *J. Anim. Sci.* 13:781-88.
- Hansard, S. L., C. L. Comar, and G. K. Davis. 1954. Effects of age upon the physiological behavior of calcium in cattle. *Am. J. Physiol.* 177:383-89.
- Hansard, S. L., C. L. Comar, and M. P. Plumlee. 1954. The effects of age upon calcium utilization and maintenance. *J. Anim. Sci.* 13:25-36.
- Hansard, S. L. and M. P. Plumlee. 1954. Effects of dietary calcium and phosphorus levels upon the physiological behavior of calcium and phosphorus in the rat. *J. Nutr.* 54:17-31.
- Comar, C. L., I. B. Whitney, and F. W. Lengemann. 1955. Comparative utilization of dietary Sr⁹⁰ and calcium by developing rat fetus and growing rat. *Proc. Soc. Exp. Biol. Med.* 88:232-36.
- Bacon, J. A., H. Patrick, and S. L. Hansard. 1956. Some effects of parathyroid extract and cortisone on metabolism of strontium and calcium. *Proc. Soc. Exp. Biol. Med.* 93:349-51.
- Mraz, F. R., M. LeNoir, J. Pinajian, and H. Patrick. 1956. Influence of parathyroid extract, cortisone and dieneestrol diacetate on metabolism of cesium in rats. *Arch. Biochem. Biophys.* 63:73-76.
- Trum, B. F. and R. H. Wasserman. 1956. Studies on the depression of radioiodine uptake by the thyroid after phenothiazine administration. II. Effect of phenothiazine on the horse thyroid. *Am. J. Vet. Res.* 17:271-75.
- Conrad, H. R. and S. L. Hansard. 1957. Effects of massive doses of vitamin D on physiological behavior of calcium in cattle. *J. Appl. Physiol.* 10:98-102.
- Lengemann, F. W. and E. W. Swanson. 1957. A study of the secretion of iodine in milk of dairy cows, using daily oral doses of I-131. *J. Dairy Sci.* 49:216-24.
- Mraz, F. R., M. LeNoir, J. J. Pinajian, and H. Patrick. 1957. Influence of potassium and sodium on uptake and retention of cesium-134 in rats. *Arch. Biochem. Biophys.* 66:177-82.
- Mraz, F. R. and H. Patrick. 1957. Organic factors controlling the excretory pattern of potassium-42 and cesium-134 in rats. *J. Nutr.* 61:535-46.
- Patrick, H. and J. A. Bacon. 1957. The effect of vitamin D upon bone mineralization of Ca⁴⁵ and Sr⁸⁹ as chlorides and as phosphopeptides. *J. Biol. Chem.* 228:569-72.
- Swanson, E. W., F. W. Lengemann, and R. A. Monroe. 1957. Factors affecting the thyroid uptake of I-131 in dairy cows. *J. Anim. Sci.* 16:318-27.
- Williams, L. G. and H. Patrick. 1957. Metabolism of cesium-134 in rabbits. *Arch. Biochem. Biophys.* 70:464-68.
- Mraz, F. R. and M. Johnson. 1958. The influence of dietary sodium, potassium and desiccated thyroid upon cesium-134 metabolism in the rat. *Endocrinology* 63:212-15.

- Reidlinger, C. R. 1958. *The development of the small intestine and its influence on the uptake of calcium-45, strontium-89, and phosphorus-32 in chick embryos*. Master's thesis, University of Tennessee.
- Cragle, R. G. and B. J. Demott. 1959. Strontium and calcium uptake and excretion in lactating dairy cows. *J. Dairy Sci.* 42:1367-72.
- Mraz, F. R. 1959. Influence of dietary potassium and sodium on cesium-134 and potassium-42 excretion in sheep. *J. Nutr.* 68:655-62.
- Demott, B. J. and R. G. Cragle. 1960. Strontium in milk. III. Distribution in cream, skim milk, cheddar cheese and whey. *J. Dairy Sci.* 43:925-30.
- Demott, B. J. and D. G. Easterly. 1960. Removal of iodine¹³¹ from milk. *J. Dairy Sci.* 43:1148-50.
- Easterly, D. G., B. J. Demott, and R. G. Cragle. 1960. Strontium in milk. I. Removal by means of reverse-flow ion exchange columns. *J. Dairy Sci.* 43:137-45.
- Easterly, D. G., B. J. Demott, and R. G. Cragle. 1960. Strontium in milk. II. Removal by batch ion exchange methods. *J. Dairy Sci.* 43:146-50.
- Mraz, F. R. and J. A. Bacon. 1960. Influence of excessive amounts of vitamin D₃ on strontium-89 metabolism in the rat. *Proc. Soc. Exp. Biol. Med.* 104:1-3.
- Bell, M. C. and R. G. Buescher. 1961. Effect of bone on Sr-89 and Ca-45 in beef roasts. *J. Am. Dieter. Assoc.* 39:567-68.
- Cragle, R. G. 1961. Uptake and excretion of cesium¹³⁴ and potassium⁴² in lactating dairy cows. *J. Dairy Sci.* 44:352-57.
- Edwards, H. M., Jr., and F. R. Mraz. 1961. Transference to egg and chick of the radio-nuclides strontium-89, calcium-45 and barium-133 when administered to laying hens. *Poult. Sci.* 40:493-503.
- Mayo, R. H. 1961. Swine metabolism unit. *J. Anim. Sci.* 20:71-73.
- Mraz, F. R. 1961. Influence of dietary calcium, phosphorus and vitamin D₃ on Ca⁴⁵, P³² and Sr⁸⁵ uptake by chicks. *J. Nutr.* 73:409-14.
- Mraz, F. R. 1961. Influence of phosphorus and some alkaline earth metals on the uptake of Ca⁴⁵, Sr⁸⁹, Ba¹³³ and P³² by tibiae of chicks. *Poult. Sci.* 40:958-65.
- Chandler, P. T. and R. G. Cragle. 1962. Gastrointestinal sites of absorption and endogenous secretion of calcium and phosphorus in dairy calves. *Proc. Soc. Exp. Biol. Med.* 111:431-34.
- Demott, B. J. and B. J. Holt. 1962. Uptake of strontium and calcium by *Streptococcus lactis*. *Nature* 193:1309-10.
- Meyer, B., J. Forrester, and M. C. Bell. 1962. Effects of three cooking methods on cesium-134 content of beef from orally dosed steers. *Food Technol.* 16:110-12.
- Mraz, F. R. 1962. Calcium and strontium uptake by rat liver and kidney mitochondria. *Proc. Soc. Exp. Biol. Med.* 111:429-31.
- Mraz, F. R. 1962. Intestinal absorption of Ca-45 and Sr-85 as affected by the alkaline earths and pH. *Proc. Soc. Exp. Biol. Med.* 110:273-75.
- Mraz, F. R. and R. G. Cragle. 1962. Influence of phosphorus and some alkaline earth metals on strontium-89 and calcium-45 excretion in the rat. *UT-ARL Report No. 3*.
- Tessmer, C. F. and D. G. Brown. 1962. Carcinoma of skin in bovine exposed to radioactive fallout. *J. Am. Med. Assoc.* 179:210-14.
- Bell, M. C. 1963. Effect of Ce¹⁴⁴-Pr¹⁴⁴ intestinal irradiation of sheep on Sr⁸⁹ and Ca⁴⁵ metabolism, p. 185. Paper presented at the 6th international congress of nutrition, held in Edinburgh, Scotland.
- Miller, J. K., E. W. Swanson, and R. G. Cragle. 1963. Effect of feeding thyroxine on secretion of I¹³¹ in milk. *J. Dairy Sci.* 46:819-24.
- Bell, M. C. and G. D. Gernon. 1964. Removal of radiocesium from beef. *Nature* 203:1189-90.
- McFee, A. F. 1964. Effects of Ce¹⁴⁴ administered to pregnant rats. *Proc. Soc. Exp. Biol. Med.* 116:712-15.
- Mraz, F. R., P. L. Wright, and T. M. Ferguson. 1964. Toxicity of high levels of calcium-45, strontium-90 and promethium-147 to avian embryos. *Proc. Soc. Exp. Biol. Med.* 116:1114-18.

- Mraz, F. R., P. L. Wright, T. M. Ferguson, and D. L. Anderson. 1964. Fission product metabolism in hens and transference to eggs. *Health Phys.* 10:777-82.
- Cragle, R. G., J. K. Miller, and P. T. Chandler. 1965. Gastrointestinal sites of absorption and secretion of Ca, P, Zn, and I in dairy cattle. In *Radioisotopes in animal nutrition and physiology*, pp. 499-515. Vienna: International Atomic Energy Agency.
- Miller, J. K., E. W. Swanson, and S. M. Hansen. 1965. Effects of feeding potassium iodide, 3,5-Diiodosalicylic acid, or L-thyroxine on iodine metabolism of lactating dairy cow. *J. Dairy Sci.* 48:942-46.
- Seigel, H. S. and F. R. Mraz. 1965. ^{131}I uptake in radiothyroidectomized chicks. *Poult. Sci.* 44:785-88.
- Downey, H. F., W. E. Stewart, R. G. Cragle, and C. S. Perry. 1966. Depletion of calcium, phosphate, and strontium from anesthetized calves by hemodialysis. *J. Dairy Sci.* 49:668-73.
- Hembry, F. G. and M. C. Bell. 1966. Sr^{90} phytate and Sr^{90} chloride in sheep and swine and roasting effect on Sr^{90} in meat. *J. Anim. Sci.* 25:199-202.
- Miller, J. K. 1966. Absorption and gastric secretion of iodine-131 and chlorine-36 in dairy calves. *Proc. Soc. Exp. Biol. Med.* 121:291-94.
- Mraz, F. R. 1966. Development of embryos and chicks administered high levels of ^{90}Sr - ^{90}Y . In *Proceedings of the 7th international congress of nutrition*, 5:841-45.
- Mraz, F. R. 1966. Embryonic response to iodine-131. *Poult. Sci.* 45:96-99.
- Pekas, J. C. 1966. Zinc-65 metabolism: Gastrointestinal secretion by the pig. *Am. J. Physiol.* 211:407-13.
- Perry, S. C., R. G. Cragle, H. F. Downey, W. E. Stewart, and C. E. Short. 1966. Effects of parathyroid extract on removal of Sr^{89} , Ca^{45} , and P^{32} by hemodialysis from conscious calves. *J. Dairy Sci.* 49:674-79.
- Bell, M. C. and C. V. Cole. 1967. *Vulnerability of food-crop and livestock production to fallout radiation*. Washington, D.C.: Office of Civil Defense and Office of the Secretary of the Army.
- Bell, M. C., R. S. Lowrey, and G. Withrow. 1967. Metabolism of strontium-89 and calcium-45 given orally to pigs 1, 3 or 7 days after whole-body irradiation. In *Strontium metabolism*, eds: J. M. A. Lenihan, J. F. Loutit, and J. H. Martin; pp. 223-27. New York: Academic Press.
- Miller, J. K. and E. W. Swanson. 1967. Performance and iodine metabolism of dairy cattle with iodine-131 irradiation injury. *J. Dairy Sci.* 50:90-95.
- Mraz, F. R., P. L. Wright, and T. M. Ferguson. 1967. Effect of dietary strontium on reproductive performance of the laying hen. In *Strontium metabolism*, eds: J. M. A. Lenihan, J. F. Loutit, and J. H. Martin; pp. 247-53. New York: Academic Press.
- Bell, M. C., M. J. Constantin, L. B. Sasser, and E. G. Siemer. 1968. *Effects of fallout radiation on agriculture*. Washington, D.C.: Office of Civil Defense and Office of the Secretary of the Army.
- Mraz, F. R. 1968. Effect of embryonic administration of ^{131}I upon reproductive performance of the White Leghorn. *Poult. Sci.* 48:916-19.
- Pekas, J. C. 1968. Zinc-65 metabolism: Effect of continuous infusion of high levels of stable zinc in swine. *J. Anim. Sci.* 27:1559-66.
- Chandler, P. T., R. G. Cragle, J. A. Bacon, and M. H. Wykoff. 1969. Absorption of ^{45}Ca and ^{89}Sr from the abomasum of the calf. *Proc. Soc. Exp. Biol. Med.* 130:1257-59.
- Cragle, R. G., W. H. Stone, J. A. Bacon, and M. H. Wykoff. 1969. Effects of large doses of orally ingested strontium-90 on young cattle. *Radiat. Res.* 37:415-22.
- Miller, J. K., B. R. Moss, and E. W. Swanson. 1969. Effects of ^{131}I thyroid irradiation damage, thyroxine, and thioxyanate on radioiodine metabolism in dairy cows. *J. Dairy Sci.* 52:677-83.
- Miller, J. K. and E. W. Swanson. 1969. Effects of Iodine-131 thyroid damage on lactation and thyroid function in the bovine. *J. Dairy Sci.* 52:95-100.
- Mraz, F. R. 1969. Calcium and strontium metabolism in Japanese and Bobwhite quail. *Poult. Sci.* 48:753-55.
- Mraz, F. R. 1969. Toxicity of high levels of zinc-65 to avian embryos. *Poult. Sci.* 48:1460-62.

- Sullivan, D. J., T. P. McDonald, and M. C. Bell. 1969. Acute radiotoxicity of ^{144}Ce - ^{144}Pr after intravenous administration to sheep. *Cornell Vet.* 59:236-49.
- Bell, M. C., L. B. Sasser, J. L. West, L. Wade, Jr., D. D. Killion, and M. J. Constantin. 1969. *Fallout radiation effects on livestock (Part A) and food crops (Part B)*. Annual report. Washington, D.C.: Office of Civil Defense and Office of the Secretary of the Army, through Division of Biology and Medicine, AEC.
- Bell, M. C., L. B. Sasser, and J. L. West. 1970. Simulated fallout radiation effects in livestock. In *Survival of food crops and livestock in the event of nuclear war*, eds: D. W. Bensen and A. H. Sparrow, pp. 193-207. New York: Brookhaven National Laboratory.
- Bell, M. C., L. B. Sasser, J. L. West, and L. Wade. 1970. Effects of feeding ^{90}Y -labeled fallout simulant to sheep. *Radiat. Res.* 43:71-82.
- Bell, M. C., L. B. Sasser, J. L. West, L. Wade, Jr., D. D. Killion, and M. J. Constantin. 1970. *Fallout radiation effects on livestock (Part A) and food crops (Part B)*. Annual report. Washington, D.C.: Office of Civil Defense and Office of the Secretary of the Army, through Division of Biology and Medicine, AEC.
- Miller, J. K. and W. F. Byrne. 1970. Absorption, excretion, and tissue distribution of orally and intravenously administered radiocerium as affected by EDTA. *J. Dairy Sci.* 53:171-75.
- Morgan, E. L. and F. R. Mraz. 1970. Effects of dietary iodine on the thyroidal uptake and elimination of ^{131}I -iodine in Coturnix and Bobwhite quail. *Poult. Sci.* 59:161-65.
- Mraz, F. R. 1970. Embryonic uptake of ^{45}Ca and ^{85}Sr . *Poult. Sci.* 49:310-11.
- Sasser, L. B., M. C. Bell, and J. L. West. 1970. Simulated fallout-radiation effects on sheep. In *Survival of food crops and livestock in the event of nuclear war*, eds: D. W. Bensen and A. H. Sparrow, pp. 178-92. New York: Brookhaven National Laboratory.
- Swanson, E. W., J. K. Miller, and R. G. Cragle. 1970. Effects of internal irradiation of the mammary gland with ^{133}Ce — ^{144}Pr . *J. Dairy Sci.* 53:46-51.
- Miller, J. K., B. R. Moss, and W. F. Byrne. 1971. Distribution of cerium in the digestive tract of the calf according to time after dosing. *J. Dairy Sci.* 54:497-502.
- Sasser, L. B., M. C. Bell, J. L. West, D. D. Killion, and M. J. Constantin. 1971. *Fallout radiation effects on livestock (Part A) and food crops (Part B)*. Annual report. Washington, D.C.: Office of Civil Defense and Office of the Secretary of the Army, through Division of Biology and Medicine.
- Wade, L., Jr., L. B. Sasser, and M. C. Bell. 1971. Effects of simulated fallout radiation on iron kinetics, red cell mass, and plasma copper in sheep. *Radiat. Res.* 46:88-89.
- Wykoff, M. H. 1971. Distribution of ^{137}Cs in the conceptus of the pregnant rat. *Radiat. Res.* 47:628-34.
- Wykoff, M. H. 1971. Distribution of strontium-85 in conceptuses of the pregnant rat. *Radiat. Res.* 48:394-401.
- Bacon, J. A. and L. Wade, Jr. 1972. A convenient method for removal of radioactive contamination in particulate form. *Health Phys.* 23:855.
- Mraz, F. R. 1972. ^{45}Ca and ^{85}Sr absorption in irradiated chickens. *Health Phys.* 22:165-68.
- Mraz, F. R. 1972. ^{45}Ca , ^{85}Sr and ^{32}P absorption by laying hens fed varying levels of calcium and phosphorus. *Poult. Sci.* 51:586-91.
- Mraz, F. R. 1972. Influence of calcium and strontium on tibial uptake of ^{45}Ca and ^{85}Sr in pullets varying in age. *Poult. Sci.* 51:968-72.
- Mraz, F. R. 1972. Influence of pre-laying dietary calcium upon tibial ^{45}Ca uptake in 20-week-old pullets. *Poult. Sci.* 51:1058-59.
- Mraz, F. R. 1972. ^{85}Sr and ^{45}Ca absorption and intestinal mitochondria uptake after perfusion with calcium and strontium. *Poult. Sci.* 51:2065-68.
- Mraz, F. R. 1972. ^{85}Sr : ^{45}Ca ratios from intestine to egg shell during perfusion with Ca and Sr. *Poult. Sci.* 51:320-25.
- Miller, J. K., W. F. Byrne, and W. A. Lyke. 1972. Comparison of fecal excretions of scandium-46 tagged sand and soluble cerium-144 by calves. *Health Phys.* 22:461-65.
- Sasser, L. B., M. C. Bell, and J. L. West. 1972. Gastrointestinal irradiation of sheep with an insoluble ^{90}Y -tagged fallout simulant. *Health Phys.* 22:467-70.
- Byrne, W. F. and M. C. Bell. 1973. *Fallout facts for beef producers*. RCD-5. Agricultural Extension Service, The University of Tennessee, and the UT-AEC Agricultural Research Laboratory of the Tennessee Agricultural Experiment Station.

- Byrne, W. F. and M. C. Bell. 1973. *Livestock; fallout and a plan for survival*. RCD-3. Extension Service, the University of Tennessee, and the UT-AEC Agricultural Research Laboratory of the University of Tennessee Agricultural Experiment Station.
- Miller, J. K., E. W. Swanson, and W. A. Lyke. 1973. Iodine concentration in nonthyroid tissues of cows. *J. Dairy Sci.* 56:1344-46.
- Mraz, F. R. 1973. Intestinal absorption of ^{45}Ca and ^{89}Sr as affected by Ca, Sr and Mg. *Poult. Sci.* 52:1208-9.
- Bell, M. C. and W. F. Byrne. 1974. *Fallout facts for swine producers*. RCD-8. Agricultural Research Laboratory of the Tennessee Agricultural Experiment Station.
- Byrne, W. F. and M. C. Bell. 1974. *Fallout facts for sheep producers*. RCD-9. Agricultural Extension Service, The University of Tennessee, and the UT-AEC Agricultural Research Laboratory of the Tennessee Agricultural Experiment Station.
- Killion, D. D. and M. J. Constantin. 1975. *Effects of fallout radiation on crop production*. ORO-747. Final report on DCPA Work Order No. DAHC 20-70-C-0312, Work Unit No. 3223F. Washington, D.C.: Defense Civil Preparedness Agency.
- Miller, J. K., E. W. Swanson, W. A. Lyke, and W. F. Byrne. 1975. Altering iodine metabolism in the calf by feeding iodine-binding agents. *J. Dairy Sci.* 58:931-37.
- Miller, J. K., E. W. Swanson, and G. E. Spalding. 1975. Iodine absorption, excretion, recycling, and tissue distribution in the dairy cow. *J. Dairy Sci.* 58:1578-93.
- Mraz, F. R. and G. R. Eisele. 1975. Increased ^{144}Ce uptake in fetal rats after the addition of carrier. *Radiat. Res.* 64:399-400.
- Mraz, F. R. and G. R. Eisele. 1977. Gastrointestinal absorption and distribution of ^{144}Ce in the suckling pig. *Health Phys.* 33:494-95.
- Mraz, F. R. and G. R. Eisele. 1977. Gastrointestinal absorption, tissue distribution, and excretion of ^{95}Nb in newborn and weanling swine and sheep. *Radiat. Res.* 72:533-36.

Note 3

Selected publications from Department of Physical Biology, Cornell University, pertinent to research stimulated by the problems of fallout (Note: Abstracts have been omitted. Publications are listed in chronological order.)

- Lengemann, F. W., C. L. Comar, and R. H. Wasserman. 1957. Absorption of calcium and strontium from milk and non-milk diets. *J. Nutr.* 61(4):571-83.
- Singer, L., M. Maqsood, A. B. Medlen and C. L. Comar. 1957. Endogenous and biliary excretion of calcium 45 and strontium 89. *Arch. Biochem. Biophys.* 66(2):404-10.
- Wasserman, R. H., F. W. Lengemann, and C. L. Comar. 1958. Comparative metabolism of calcium and strontium in lactation. *J. Dairy Sci.* 41(6):812-921.
- Lengemann, F. W., R. H. Wasserman, and C. L. Comar. 1959. Studies on the enhancement of radiocalcium and radiostrontium absorption by lactose in the rat. *J. Nutr.* 68(3):443-56.
- Wasserman, R. H. and C. L. Comar. 1959. Carbohydrates and the gastrointestinal absorption of radiostrontium and radiocalcium in the rat. *Proc. Soc. Exp. Biol. Med.* 101(2):314-317.
- Wasserman, R. H., A. R. Twardock, and C. L. Comar. 1959. Metabolic dissociation of short-lived barium-137m from its cesium-137 parent. *Science* 129(3348):568-69.
- Comar, C. L. and R. H. Wasserman. 1960. Radioisotope absorption and methods of elimination: Differential behavior of substances in metabolic pathways. In *Radioisotopes in the biosphere*, eds: R. S. Caldecott and L. A. Snyder, pp. 526-40. Minneapolis, Minn.: Univ. of Minn., Center for Continuation Study.
- Lengemann, F. W. 1960. The effect of whole-body x-irradiation on the absorption of calcium-45 and strontium-85 from the intestinal tract of the rat. *Radiat. Res.* 13(6):892-97.
- Lengemann, F. W. 1960. Studies on the discrimination against strontium by bone grown in vitro. *J. Biol. Chem.* 235(7):1859-62.
- Lengemann, F. W., R. H. Wasserman, and C. L. Comar. 1960. The effect of growth and thyroid hormones upon the removal by lavage of calcium and strontium from the skeleton of the rat. *Endocrinology* 67(4):535-39.

- Lough, S. A., G. H. Hamada, and C. L. Comar. 1960. Secretion of dietary strontium-90 and calcium in human milk. *Proc. Soc. Exp. Biol. Med.* 104(2):194-98.
- Okonski, J., F. W. Lengemann, and C. L. Comar. 1960. The utilization of egg iodine by the chicken embryo. *J. Exp. Zool.* 145(3):263-69.
- Raven, A. M., F. W. Lengemann, and R. H. Wasserman. 1960. Studies of the effect of lysine on the absorption of radiocalcium and radiostrontium by the rat. *J. Nutr.* 72(1):29-36.
- Twardock, A. R., W. H. Prinz, and C. L. Comar. 1960. The state of calcium and strontium in goat's milk. *Arch. Biochem. Biophys.* 89(2):309-12.
- Wasserman, R. H. 1960. Metabolic basis of calcium and strontium discrimination: Studies with surviving intestinal segments. *Proc. Soc. Exp. Biol. Med.* 104(1):92-95.
- Wasserman, R. H. 1960. Radioisotope absorption and methods of elimination: A critical review. In *Radioisotopes in the biosphere*, eds: R. S. Caldecott and L. A. Snyder, pp. 564-76. Minneapolis, Minn.: Univ. of Minn., Center for Continuation Study.
- Wasserman, R. H. and C. L. Comar. 1960. Effect of dietary calcium and phosphorus levels on body burdens of ingested radiostrontium. *Proc. Soc. Exp. Biol. Med.* 103(1):124-29.
- Wasserman, R. H. and C. L. Comar. 1960. Effectiveness of dietary substances in reducing the retention of chronically ingested radiostrontium; studies with tannin. *Nature* 185:629-30.
- Wasserman, R. H. and F. W. Lengemann. 1960. Further observations on lactose stimulation of the gastrointestinal absorption of calcium and strontium in the rat. *J. Nutr.* 70(3):377-84.
- Comar, C. L. and J. R. Georgi. 1961. Assessment of chronic exposure to radiostrontium by urinary assay. *Nature* 199:390-91.
- Comar, C. L., R. H. Wasserman, and A. R. Twardock. 1961. Secretion of calcium and strontium into milk. *Health Phys.* 7:69-80.
- Hogue, D. E., W. G. Pond, C. L. Comar, L. T. Alexander, and E. P. Hardy. 1961. Comparative utilization of dietary calcium and strontium-90 by pigs and sheep. *J. Anim. Sci.* 20(3):514-17.
- Lengemann, F. W. and C. L. Comar. 1961. Distribution of absorbed Sr^{85} and Ca^{45} as influenced by lactose. *Am. J. Physiol.* 200(5):1051-54.
- Lengemann, F. W. and C. L. Comar. 1961. The effect of whole-body x-irradiation upon the passage and absorption of strontium and calcium in the gastrointestinal tract of the rat. *Radiat. Res.* 14(5):662-67.
- Monroe, R. A., R. H. Wasserman, and C. L. Comar. 1961. Comparative behavior of strontium-calcium and cesium-potassium in the fowl. *Am. J. Physiol.* 200(3):535-38.
- Okonski, J., F. W. Lengemann, and C. L. Comar. 1961. Incorporation of I-131 into chicken eggs. *Health Phys.* 6:27-31.
- Twardock, A. R. and C. L. Comar. 1961. Calcium and strontium secretion from blood to milk. *Am. J. Physiol.* 201(4):645-50.
- Wasserman, R. H. and C. L. Comar. 1961. *Annotated bibliography of strontium and calcium metabolism in man and animals*. Misc. publ. no. 821. Washington, D.C.: U.S. Department of Agriculture.
- Wasserman, R. H. and C. L. Comar. 1961. The influence of dietary potassium on the retention of chronically ingested cesium-137 in the rat. *Radiat. Res.* 15(1):70-77.
- Wasserman, R. H. and C. L. Comar. 1961. The parathyroids and the intestinal absorption of calcium, strontium and phosphate ions in the rat. *Endocrinology* 69(6):1074-79.
- Wasserman, R. H., F. A. Kallfelz, and C. L. Comar. 1961. Active transport of calcium by rat duodenum in vivo. *Science* 133(3456):883-84.
- Binnerts, W. T., F. W. Lengemann, and C. L. Comar. 1962. Radioiodine metabolism in the goat after simultaneous single and daily administration. *J. Dairy Sci.* 45(3):427-29.
- Lengemann, F. W. 1962. Distribution of radiostrontium and radiocesium in milk and milk products. *J. Dairy Sci.* 45(4):538-39.
- Lengemann, F. W. 1962. Effects of thyroxine upon strontium and calcium metabolism of embryonic bone grown in vitro. *Endocrinology* 70(6):774-80.
- Marcus, C. S. and F. W. Lengemann. 1962. Absorption of Ca^{45} and Sr^{85} from solid and liquid food at various levels of the alimentary tract of the rat. *J. Nutr.* 77(2):155-60.

- Moore, W., Jr., and C. L. Comar. 1962. Absorption of caesium-137 from the gastrointestinal tract of the rat. *Int. J. Radiat. Biol. & Relat. Stud. Phys. Chem. & Med.* 5(3):247-54.
- Moore, W., Jr., C. L. Comar, and R. H. Wasserman. 1962. Cesium, strontium and calcium metabolism. Some recent developments. In *The use of radioisotopes in animal biology and medical sciences*, ed. J. Frieden, vol. 2, pp. 117-36. New York: Academic Press.
- Nold, M. M., D. N. Tapper, and C. L. Comar. 1962. Cs-137 dose measurements in tissue II. *Health Phys.* 8:217-29.
- Tapper, D. N., M. M. Nold, and C. L. Comar. 1962. Cs-137 dose measurements in tissue I. *Health Phys.* 8:207-16.
- Wasserman, R. H., C. L. Comar, and A. R. Twardock. 1962. Metabolic behavior of ^{137}Cs - ^{137m}Ba in the lactating goat. *Int. J. Radiat. Biol. & Relat. Stud. Phys. Chem. & Med.* 4(3):299-310.
- Comar, C. L. 1963. Factors influencing the biological availability of fallout radionuclides for animals and man. *Fed. Proc.* 22(6), pt. 2:1402-9.
- Comar, C. L. 1963. Some over-all aspects of calcium-strontium discrimination. In *Transfer of calcium and strontium across biological membranes*, ed. R. H. Wasserman, pp. 405-17. New York: Academic Press.
- Comar, C. L., S. A. Goldblith, H. F. Kraybill, R. F. Reitemeier, and R. E. Shank. 1963. *Radionuclides in foods*. National Academy of Sciences-National Research Council, publ. 988. Revised in *Health Phys.* 9:569-96.
- Comar, C. L. and R. H. Wasserman. 1963. Strontium. In *Mineral metabolism*, eds. C. L. Comar and F. Bronner, vol. 2A, pp. 523-72. New York: Academic Press.
- Lengemann, F. W. 1963. ^{131}I concentrations in blood, milk, urine and faeces of dairy cows following a single dose of radio-iodine. *J. Agri. Sci.* 61:375-79.
- Lengemann, F. W. 1963. Over-all aspects of calcium and strontium absorption. In *Transfer of calcium and strontium across biological membranes*, ed. R. H. Wasserman, pp. 85-96. New York: Academic Press.
- Lengemann, F. W. 1963. Some effects of parathyroid hormone on the metabolism of Sr^{85} and Ca^{45} by embryonic chick bone culture in vitro. *Endocrinology* 72:364-69.
- Lengemann, F. W. and C. L. Comar. 1963. Fluoridated water and the skeletal uptake of Sr^{85} and Ca^{45} by young rats. *J. Nutr.* 79(2):195-99.
- Lough, S., J. Rivera, and C. L. Comar. 1963. Retention of strontium, calcium and phosphorus in human infants. *Proc. Soc. Exp. Biol. Med.* 112:631-36.
- Mercer, P. F., N. H. Mercer, and R. H. Wasserman. 1963. Autoradiographic distribution patterns reflecting the concentrating mechanism in rat kidney. *The Physiologist* 6.
- Moore, W., Jr., and C. L. Comar. 1963. Movement of ^{137}Cs across surviving intestinal segments in vitro. *Int. J. Radiat. Biol. & Relat. Stud. Phys. Chem. & Med.* 6(6):507-11.
- Wasserman, R. H., C. L. Comar, and D. N. Tapper. 1963. Influence of dietary potassium and sodium on cesium-137 retention in rats. *Proc. Soc. Exp. Biol. Med.* 113:305-7.
- Wasserman, R. H. 1963. Vitamin D and the absorption of calcium and strontium in vivo. In *Transfer of calcium and strontium across biological membranes*, ed. R. H. Wasserman, pp. 211-28. New York: Academic Press.
- Lengemann, F. W. and C. L. Comar. 1964. Metabolism of ^{131}I by dairy cows during long-term daily administration of the radioisotope. *Health Phys.* 10:55-59.
- Comar, C. L., K. Kostial, N. Gruden, and G. E. Harrison. 1965. Metabolism of strontium in the newborn. *Health Phys.* 11:609-15.
- Giese, W., F. W. Lengemann, and R. A. Wentworth. 1965. A mathematical evaluation of the excretion curves of iodine-131 in milk of cows. In *Radioisotopes in animal nutrition and physiology*, pp. 221-30. Vienna: International Atomic Energy Agency.
- Kostial, K., S. Vojvodic, and C. L. Comar. 1965. Effects of dietary levels of phosphorus and calcium on the comparative behaviour of strontium and calcium. *Nature* 208:1110.
- Lengemann, F. W. 1965. Factors affecting iodine concentration in bovine milk. *J. Dairy Sci.* 48(2):197-202.
- Lengemann, F. W. 1965. The study of iodine secretion into the milk of dairy animals. In *Radioisotopes in animal nutrition and physiology*, pp. 203-20. Vienna: International Atomic Energy Agency.

- Marcus, C. S. and R. H. Wasserman. 1965. Comparison of intestinal discrimination between calcium-47, strontium-85, and barium-133. *Am. J. Physiol.* 209:973.
- Wasserman, R. H., F. W. Lengemann, J. C. Thompson, Jr., and C. L. Comar. 1965. The transfer of fallout radionuclides from diet to man. In *Radioactive fallout; soils, plants, foods, man*, ed. E. B. Fowler, pp. 204-44. Amsterdam: Elsevier Press.
- Comar, C. L. 1966. Radioactive materials in animals—entry and metabolism. In *Radioactivity and human diet*, chapter 7.
- Comar, C. L. 1966. Transfer of strontium-90 into animal produce. In *Radioactivity and human diet*, chapter 12.
- Comar, C. L. and F. W. Lengemann. 1966. General principles of the distribution and movement of artificial fallout through the biosphere to man. *Radioecological concentration processes*.
- Comar, C. L., R. H. Wasserman, and F. W. Lengemann. 1966. Effect of dietary calcium on secretion of strontium into milk. *Health Phys.* 12:1.
- Comar, C. L., R. H. Wasserman, A. R. Twardock, and F. W. Lengemann. 1966. Effect of various substances on secretion of radiostrontium into milk. *Health Phys.* 12:1661-69.
- Lengemann, F. W. 1966. Predicting the total projected intake of radioiodine from milk by man-I. *Health Phys.* 12:825-30.
- Lengemann, F. W. 1966. Predicting the total projected intake of radioiodine from milk by man-II. *Health Phys.* 12:831-35.
- Comar, C. L. 1967. Some principles of strontium metabolism: Implications, applications, limitations. In *Strontium metabolism*, eds. J. M. Lenihan, J. F. Loutit, and J. H. Martin. New York-London: Academic Press.
- Kallfelz, F. A., A. N. Taylor, and R. H. Wasserman. 1967. Vitamin D-induced calcium binding factor in rat intestinal mucosa. *Proc. Soc. Exp. Biol. Med.* 125:54-58.
- Thompson, J. C., Jr. and C. L. Comar. 1967. Estimation of dietary strontium-90 by urinary assay. Applied and theoretical aspects. *Health Phys.* 13:5-13.
- Anderson, J. J. B. and C. L. Comar. 1968. Strontium retention as a function of age in the dog. *Radiat. Res.* 34:153-69.
- Corradino, R. A., R. H. Wasserman, M. H. Pubols, and S. I. Chang. 1968. Vitamin D₃ induction of a calcium-binding protein in the uterus of the laying hen. *Arch. Biochem. Biophys.* 125(1):378-80.
- Ebel, J. G. and C. L. Comar. 1968. Effect of dietary magnesium on strontium-calcium discrimination and incorporation into bone of rats. *J. Nutr.* (3):403-8.
- Thompson, J. C., Jr. 1968. Comparison of iodine-131 intake from milk and non-milk foods. *Health Phys.* 14:483-88.
- Wasserman, R. H. 1968. Calcium transport by the intestine: A model and comment on vitamin D action. *Calcif. Tissue Res.* 2:301-13.
- Wasserman, R. H., R. A. Corradino, and A. N. Taylor. 1968. Vitamin D-dependent calcium-binding protein. Purification and some properties. *J. Biol. Chem.* 243:3978-86.
- Wasserman, R. H. and A. N. Taylor. 1968. Vitamin D-dependent calcium-binding protein: Response to some physiological and nutritional variables. *J. Biol. Chem.* 243:3978-93.
- Taylor, A. M., R. H. Wasserman. 1969. Correlations between the vitamin D-induced calcium binding protein and intestinal absorption of calcium. *Fed. Proc.* 28:1834-38.
- Ebel, J. G. and C. L. Comar. 1969. Use of Sr-Ca ratios in hair for monitoring. *Health Phys.* 16:205-8.
- Lengemann, F. W. 1969. Metabolism of radioiodide by lactating goats given iodine-131 for extended periods. *J. Dairy Sci.* 53:165-70.
- Lengemann, F. W. 1969. Radioiodine in the milk of cows and goats after oral administration of radioiodate and radioiodide. *Health Phys.* 17:565-69.
- Lengemann, F. W. 1969. Retention of radiocesium by rats before and after weaning. *J. Nutr.* 99:419-24.
- Wasserman, R. H., R. A. Corradino, and A. N. Taylor. 1969. Binding proteins from animals with possible transport function. *J. Gen. Physiol.* 54:114-34.

- Wasserman, R. H. and A. N. Taylor. 1969. Some aspects of the intestinal absorption of calcium with special reference to vitamin D. In *Mineral metabolism*, vol. 5, pt. 3, eds. C. L. Comar and F. Bronner, pp. 321-403. New York: Academic Press.
- Corradino, R. A. and R. H. Wasserman. 1970. Strontium inhibition of vitamin D₃-induced calcium-binding protein (CaBP) and calcium absorption in chick intestine. *Proc. Soc. Exp. Biol. Med.* 133:960-63.
- Lengemann, F. W. 1970. ¹³⁴Cs retention in rats from one to 25 months of age. *Radiat. Res.* 42:169-74.
- Lengemann, F. W. 1970. Interaction of temperature, age and sex on the retention of radio-cesium by rats. *Health Phys.* 19:785-90.
- Morrissey, R. L. and R. H. Wasserman. 1970. Adaptation, calcium binding protein (CaBP) and the intestinal absorption of calcium. *Fed. Proc.* 29.
- Wasserman, R. H. 1970. The vitamin D-dependent calcium-binding protein. In *The fat-soluble vitamins*, eds. H. F. DeLuca and J. W. Suttie, pp. 21-37. The Univ. of Wisconsin Press.
- Corradino, R. A., J. G. Ebel, P. H. Craig, A. N. Taylor, and R. H. Wasserman. 1971. Calcium absorption and the vitamin D₃-dependent calcium-binding protein. I. Inhibition by dietary strontium. *Calcif. Tissue Res.* 7:81-92.
- Corradino, R. A., J. G. Ebel, P. H. Craig, A. N. Taylor, and R. H. Wasserman. 1971. Calcium absorption and the vitamin D₃-dependent calcium-binding protein. II. Recovery from dietary strontium inhibition. *Calcif. Tissue Res.* 7:93-102.
- Corradino, R. A. and R. H. Wasserman. 1971. Vitamin D₃: Induction of calcium-binding protein in embryonic chick intestine in vitro. *Science* 172:731-33.
- Ingersoll, R. J. and R. H. Wasserman. 1971. Vitamin D₃-induced calcium-binding protein: Binding characteristics, conformational effects, and other properties. *J. Biol. Chem.* 246(9):2808-14.

Note 4

- A. Formulas for placental discrimination (from Wasserman et al. 1957 and Comar and Wasserman 1960).

$$DF_{\text{absorptive}} = \frac{100 - F_{\text{Sr}}}{100 - F_{\text{Ca}}}$$

$$DF_{\text{urinary}} = \frac{(100 - F_{\text{Ca}}) - \left[U_{\text{Sr}} \times \frac{100 - F_{\text{Ca}}}{100 - F_{\text{Sr}}} \right]}{M_{\text{Ca}} + P_{\text{Ca}}}$$

$$DF_{\text{placental-dam}} = \left[\frac{M_{\text{Sr}}}{M_{\text{Ca}}} \right] \left[\frac{M_{\text{Ca}} + P_{\text{Ca}}}{M_{\text{Sr}} + P_{\text{Sr}}} \right]$$

$$DF_{\text{placental-fetus}} = \left[\frac{P_{\text{Sr}}}{P_{\text{Ca}}} \right] \left[\frac{M_{\text{Ca}} + P_{\text{Ca}}}{M_{\text{Sr}} + P_{\text{Sr}}} \right]$$

Where:

- $F_{\text{Sr}}, F_{\text{Ca}}$ = % of ingested Sr or Ca in feces
 $M_{\text{Sr}}, M_{\text{Ca}}$ = % of ingested Sr or Ca in dam
 $P_{\text{Sr}}, P_{\text{Ca}}$ = % of ingested Sr or Ca in fetus
 $U_{\text{Sr}}, U_{\text{Ca}}$ = % of ingested Sr or Ca in urine

B. Formulas for lactational discrimination (from Wasserman, Lengemann, and Comar 1958, and Comar and Wasserman 1960).

$$DF_{\text{absorptive}} = \frac{100 - F_{\text{Sr}}}{100 - F_{\text{Ca}}}$$

$$DF_{\text{urinary}} = \frac{(100 - F_{\text{Ca}}) - \left[U_{\text{Sr}} \times \frac{100 - F_{\text{Ca}}}{100 - F_{\text{Sr}}} \right]}{B_{\text{Ca}} + L_{\text{Ca}}}$$

$$DF_{\text{lactational-body}} = \left[\frac{B_{\text{Sr}}}{B_{\text{Ca}}} \right] \left[\frac{B_{\text{Ca}} + L_{\text{Ca}}}{B_{\text{Sr}} + L_{\text{Sr}}} \right]$$

$$DF_{\text{lactational-milk}} = \left[\frac{L_{\text{Sr}}}{L_{\text{Ca}}} \right] \left[\frac{B_{\text{Ca}} + L_{\text{Ca}}}{B_{\text{Sr}} + L_{\text{Sr}}} \right]$$

Where:

$F_{\text{Sr}}, F_{\text{Ca}}$ = % of ingested Sr or Ca in feces

$B_{\text{Sr}}, B_{\text{Ca}}$ = % of ingested Sr or Ca in body

$L_{\text{Sr}}, L_{\text{Ca}}$ = % of ingested Sr or Ca in milk

$U_{\text{Sr}}, U_{\text{Ca}}$ = % of ingested Sr or Ca in urine

References

- Åberg, B. and F. P. Hungate, eds. 1967. *Radioecological concentration processes*. Proceedings of an international symposium held in Stockholm, April 25-29, 1966, Oxford-London-New York: Pergamon Press.
- Adams, W. H., C. W. Christenson, and E. B. Fowler. 1965. Relationship of soil, plant and radionuclide. In Fowler 1965, pp. 30-51.
- Alexander, G. V., R. E. Nusbaum, and N. S. MacDonald. 1956. The relative retention of strontium and calcium in bone tissue. *J. Biol. Chem.* 218:911-19.
- Alexander, L. T., E. P. Hardy, Jr., and H. L. Hollister. 1960. Radioisotopes in soils: Particularly with reference to strontium. In Caldecott and Snyder, pp. 3-22.
- Andrews, H. L. and S. Warren. 1969. Ion scavenging by the eastern clam and quahog. *Health Phys.* 17:807-10.
- Arneil, G. C. 1967. Studies in strontium metabolism 3: Preferential calcium-strontium renal tubular absorption measured by activation analysis. In Lenihan, Loutit, and Martin, pp. 67-70.
- Auerbach, S. I. 1957. Data presented at a Health Physics advisory board meeting, held at Oak Ridge National Laboratory, November 1957. [Quoted by Langham and Anderson 1959.]
- Auerbach, S. I. and D. A. Crossley, Jr., eds. 1958. Strontium-90 and cesium-137 uptake by vegetation under natural conditions. In *Proceedings of the 2d United Nations international conference on the peaceful uses of atomic energy*, vol. 18, pp. 494-99. Held in Geneva, September 1-13, 1958. Geneva: United Nations.
- Bauer, G. C. H., A. Carlsson, and B. Lindquist. 1955. A comparative study on the metabolism of Sr^{90} and Ca^{45} . *Acta Physiol. Scand.* 35:56-66.
- Bell, M. C., R. S. Lowrey, and G. Winthrow. 1967. Metabolism of strontium-89 and calcium-45 given orally to pigs 1, 3 or 7 days after whole-body irradiation. In Lenihan, Loutit, and Martin 1967, pp. 223-27.

- Beninson, F., H. Migliori, and E. Ramos. 1964. *Fallout program quarterly summary report*. HASL-149. New York: U.S. Atomic Energy Commission, New York Operations Office.
- Biddulph, O. 1960. Radioisotopes in plants: Foliar entry and distribution. In Caldecott and Snyder 1960, pp. 73-85.
- Black, S. C., D. N. McNelis, and E. W. Bretthauer. 1972. *Radionuclide studies in dairy cows following Project Schooner*. SWRHL-112-r. Las Vegas: Southwestern Radiological Health Laboratory.
- Black, S. C., R. E. Engel, V. W. Randecker, and D. S. Barth. 1971. *Radioiodine studies in dairy cows following Project Palanquin*. PNE-914F. Las Vegas: Southwestern Radiological Health Laboratory.
- Blume, J. M., C. E. Hagen, and R. W. Mackie. 1950. Radiation injury to plants grown in nutrient solutions containing P^{32} . *Soil Sci.* 70:415-26.
- Book, S. A., D. A. McNeill, N. J. Parks, and W. L. Spangler. 1980. Comparative effects of iodine-132 and iodine-131 in rat thyroid glands. *Radiat. Res.* 81:246-53.
- Boroughs, H., W. A. Chipman, and T. R. Rice. 1957. Laboratory experiments on the uptake, accumulation, and loss of radionuclides by marine organisms. Chapter 8 in NAS-NRC 1957, pp. 80-87.
- Brown, D. G., R. A. Reynolds, and D. F. Johnson. 1966. Late effects in cattle exposed to radioactive fallout. *Am. J. Vet. Res.* 27:1509-14.
- Brungs, W. A. 1965. Experimental uptake of strontium-85 by fresh-water organisms. *Health Phys.* 11:41-46.
- Bukovac, M. J., S. H. Wittwer, and H. B. Tukey. 1965. Aboveground plant parts as a pathway for entry of fission products into the food chain with special reference to $^{89-90}\text{Sr}$ and ^{137}Cs . In Fowler 1965, pp. 82-109.
- Caldecott, R. S. and L. A. Snyder, eds. 1960. *Radioisotopes in the biosphere*. Proceedings of a symposium held in Minneapolis, October 19-23, 1959. Minneapolis: Univ. of Minn., Center for Continuation Study.
- Casarett, A. P. 1968. *Radiation biology*, especially chapter 13. Englewood Cliffs, N.J.: Prentice-Hall, Inc.
- Cataldo, D. A., E. L. Klepper, and D. K. Craig. 1976. Fate of plutonium intercepted by leaf surfaces: Leachability and translocation to seed and root tissues. In *Transuranium nuclides in the environment*, pp. 291-301. Proceedings of a symposium held in San Francisco, November 17-21, 1975. Vienna: International Atomic Energy Agency.
- Cataldo, D. A. and B. E. Vaughan. 1980. Interaction of airborne plutonium with plant foliage. In Hanson 1980, pp. 288-99.
- Clark, I., E. A. Gusmano, R. Nevins, and S. H. Cohn. 1964. Effect of magnesium on uptake and retention of radioactive strontium. *Proc. Soc. Exp. Biol. Med.* 116:984-87.
- Cline, J. F. and F. P. Hungate. 1956. Effect of strontium and calcium in soil on uptake of Sr^{90} by barley plants. In *Biology research annual report 1955*. HW-41500, pp. 7-13. Richland, Wash.: Hanford Works.
- Cohn, S. H. 1961. Effect of aging and x-irradiation on the kinetics of skeletal metabolism in the rat. *Radiat. Res.* 15:355-65.
- Cohn, S. H. 1982. Taped interview at Brookhaven National Laboratory, September 16, 1982.
- Cohn, S. H. and E. A. Gusmano. 1963. Uptake and transfer of fallout I^{131} in pregnant women. *Health Phys.* 9:1267-69.
- Cohn, S. H. and E. A. Gusmano. 1967. Kinetics of strontium and calcium skeletal metabolism in the rat. *Proc. Soc. Exp. Biol. Med.* 126:79-83.
- Cohn, S. H., S. Nobel, and A. E. Sobel. 1961. Diet-induced changes in the exchange and accretion of radiostrontium by rat skeleton. *Radiat. Res.* 15:59-69.
- Cohn, S. H., J. S. Robertson, and R. A. Conard. 1960. Radioisotopes and environmental circumstances: The internal radioactive contamination of a Pacific island community exposed to local fallout. In Caldecott and Snyder 1960, pp. 306-30.
- Cohn, S. H., S. R. Bozzo, J. E. Jesseph, C. Constantinides, E. A. Gusmano, and J. S. Robertson. 1966. Strontium and calcium skeletal discrimination determined by compartmental analysis. *J. Appl. Physiol.* 21:67-72.

- Cohn, S. H., S. W. Lippincott, E. A. Gusmano, and J. S. Robertson. 1963a. Comparative kinetics of Ca^{47} and Sr^{85} in man. *Radiat. Res.* 19:104-19.
- Cohn, S. H., B. Rosoff, E. A. Gusmano, and H. Spencer. 1963b. II. Long-term Cs^{137} turnover in man as measured by a whole-body counter. *Radiat. Res.* 19:655-58.
- Cohn, S. H., H. Spencer, J. Samachson, A. Feldstein, and E. A. Gusmano. 1962a. Influence of dietary stable strontium and calcium on the turnover of bone-fixed Sr^{85} in man. *Proc. Soc. Exp. Biol. Med.* 110:526-28.
- Cohn, S. H., H. Spencer, J. Samachson, and J. S. Robertson. 1962b. The turnover of strontium-85 in man as determined by whole-body counting. *Radiat. Res.* 17:173-85.
- Comar, C. L. 1953a. Isotope methodology and miscellaneous agricultural applications. In *The role of atomic energy in agricultural research*, eds. C. L. Comar and S. L. Hood, TID-5115, pp. 151-70. [This paper contains numerous references to earlier work organized by subject heading.] Proceedings of the 4th annual Oak Ridge summer symposium held August 25-30, 1952. Oak Ridge, Tenn.: Oak Ridge National Laboratory, Oak Ridge Institute of Nuclear Studies.
- Comar, C. L. 1953b. Skeletal metabolism studies with radiocalcium. In *The role of atomic energy in agricultural research*, eds. C. L. Comar and S. L. Hood, TID-5115, pp. 225-39. Proceedings of the 4th annual Oak Ridge summer symposium held August 25-30, 1952. Oak Ridge, Tenn.: Oak Ridge National Laboratory, Oak Ridge Institute of Nuclear Studies.
- Comar, C. L. 1967. Some principles of strontium metabolism: Implications, applications, limitations. In Lenihan, Loutit, and Martin 1967, pp. 17-30.
- Comar, C. L., W. E. Lotz, and G. A. Boyd. 1952. Autoradiographic studies of calcium, phosphorus and strontium distribution in the bones of the growing pig. *Am. J. Anat.* 90:113-29.
- Comar, C. L., R. S. Russell, and R. H. Wasserman. 1957. Strontium-calcium movement from soil to man. *Science* 126:485-92.
- Comar, C. L. and R. H. Wasserman. 1960. Radioisotope absorption and methods of elimination: Differential behavior of substances in metabolic pathways. In Caldecott and Snyder 1960, pp. 526-40.
- Comar, C. L., R. H. Wasserman, and M. M. Nold. 1956. Strontium-calcium discrimination factors in the rat. *Proc. Soc. Exp. Biol. Med.* 92:859-63.
- Cooper, E. P. 1969. Draft report, *Disposition of Naval Radiological Defense Laboratory. Technical staff and program with historical notes*. Official use only. October 31, 1969.
- Cooper, E. P. 1983. Personal interview at Naval Ocean Systems Center, San Diego, Calif., July 29, 1983.
- Cutshall, N. 1974. Turnover of zinc-65 in oysters. *Health Phys.* 26:327-31.
- Dahlman, R. C., S. I. Auerbach, and P. B. Dunaway. 1969. Behaviour of ^{137}Cs -tagged particles in a fescue meadow. In *Environmental contamination by radioactive materials*, pp. 153-65. Proceedings of a symposium held in Vienna, March 24-28, 1969. Vienna: International Atomic Energy Agency.
- Daley, E. M. and D. D. Smith. 1969. *Agronomic aspects of the experimental dairy farm, January 1966-December 1968*. SWRHL-63r. Las Vegas: Southwestern Radiological Health Laboratory.
- Della Rosa, R. J., F. A. Smith, and J. N. Stannard. 1961. The renal excretion of strontium and calcium in dogs. *Int. J. Radiat. Biol. & Relat. Stud. Phys. Chem. & Med.* 3:557-78.
- Department of Health, Education and Welfare. 1966. *Radiological health research*. Summary report of National Center for Radiological Health for period July 1965-December 1966. Publ. no. 1672. Washington, D.C.: Public Health Service.
- DHEW. See U.S. Department of Health, Education and Welfare.
- Donaldson, L. R. and R. F. Foster. 1957. Effects of radiation on aquatic organisms. Chapter 10 in NAS-NRC 1957, pp. 96-102.
- Doniach, I. 1957. Comparison of the carcinogenic effect of x-irradiation with radioactive iodine on the rat thyroid. *Br. J. Cancer* 11:67-76.

- Douglas, R. L., S. C. Black, and D. S. Barth. 1971. ¹³⁷I transport through the air-forage-cow-milk system using an aerosol mist (Project Rainout). SWRHL-43-r. Las Vegas: Southwestern Radiological Health Laboratory.
- Dumont, P. A., P. F. Curran, and A. K. Solomon. 1960. Calcium and strontium in rat small intestine, their fluxes and their effect on sodium flux: *J. Gen. Physiol.* 43:1119-36.
- Durbin, P. W., N. Jeung, M. H. Williams, and M. W. Parrot. 1974. Long-term metabolism of ⁹⁰Sr in rhesus monkeys (*Macaca mulatta*). In *Proceedings of the 3d international congress of the International Radiation Protection Association*, ed. W. S. Snyder, CONF-730907-P2, pp. 1412-17. Held in Washington, D.C., September 9-14, 1973. Oak Ridge, Tenn.: Technical Information Center.
- Eberhardt, L. L. 1967. Relationship of cesium-137 half-life in humans to body weight. *Health Phys.* 13:88-90.
- Ehrler, W. L., A. H. Lange, and C. C. Hamner. 1955. *The effect of certain environmental factors on mineral uptake by bean plants. I. Phosphorus uptake.* AEC report UCLA-328. Univ. of Calif. at Los Angeles.
- Ehrler, W. L., E. M. Romney, and C. C. Hamner. 1955. *The effect of certain environmental factors on calcium, phosphorus, and strontium uptake by barley.* AEC report UCLA-351. Univ. of Calif. at Los Angeles.
- Eisenbud, M. 1973. *Environmental radioactivity.* New York-London: Academic Press.
- Engstrom, A., R. Bjornerstedt, C. J. Clemedson, and A. Nelson. 1957. *Bone and radio-strontium.* New York-Almqvist and Wiksell, Stockholm: John Wiley & Sons.
- Erf, L. A. and C. Pecher. 1940. Secretion of radio-strontium in milk of two cows following intravenous administration. *Proc. Soc. Exp. Biol. Med.* 45:762-64.
- Essington, E., H. Nishita, and A. Wallace. 1961. *Influence of chelates on availability of fission products to plants grown in a contaminated soil.* AEC report UCLA-475. Univ. of Calif. at Los Angeles. [Also *Soil Sci.* 94:96-105 (1962); and E. Essington, H. Nishita, and A. Wallace 1963. Effect of chelating agents on the uptake of Y⁹¹, Ru¹⁰⁶, Ce¹⁴⁴ and Pm¹⁴⁷ by beans grown in a calcareous soil. *Soil Sci.* 95:331-37.]
- Finkel, M. P. 1958. Mice, men, and fallout. *Science* 128:637-41.
- Finkel, M. P., B. O. Biskis, and P. J. Bergstrand. 1960. Radioisotope toxicity: Significance of chronic administration. In Caldecott and Snyder 1960, pp. 461-73.
- Finkel, M. P., B. O. Biskis, J. Greco, and R. W. Candem. 1972. Strontium-90 toxicity in dogs: Status of Argonne study on influence of age and dosage pattern. In Goldman and Bustad 1972, pp. 285-312.
- Fowler, E. B., ed. 1965. *Radioactive fallout, soils, plants, foods, man.* Amsterdam-London-New York: Elsevier Publishing Co.
- Fredrikson, L., B. Eriksson, B. Rasmuson, B. Gahne, K. Edvarson, and K. Löw. 1958. Studies of soil-plant-animal interrelationships with respect to fission products. In *Proceedings of the 2d United Nations international conference on the peaceful uses of atomic energy*, vol. 18, pp. 449-70. Held in Geneva, September 1-13, 1958. Geneva: United Nations. Also in *Progress in nuclear energy*, vol. 1, Health Physics, 500-545. New York-London: Pergamon Press.
- Fried, M. and W. R. Heald. 1960. Radioisotopes in soils: Soil-plant relationship. In Caldecott and Snyder 1960, pp. 47-59.
- Furchner, J. E. and G. A. Drake. 1973. Disposition of cesium-137 during potassium depletion in rats. In *Annual report of the Biomedical and Environmental Research Program of the LASL Health Division*, LA-5633-PR, pp. 14-15. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Furchner, J. E., G. A. Drake, and C. R. Richmond. 1964. The lack of effect of water loading on the retention of cesium-137 by rats. In *Annual report of Health Division*, LAMS-3132, pp. 37-41. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Furchner, J. E. and C. R. Richmond. 1963. Effect of environmental temperatures on retention of cesium 137 by mice: *J. Appl. Physiol.* 18:786-88.
- Furchner, J. E., C. R. Richmond, and G. A. Drake. 1964. The effect of temperature on the retention of ruthenium-106 and manganese-54 by mice. In *Annual report of Health Division*, LAMS-3132, pp. 32-36. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.

- Furchner, J. E., C. R. Richmond, and G. A. Drake. 1965. Effects of environmental temperature on retention of chronically administered cesium-137. *Health Phys.* 11:623-28.
- Furchner, J. E., C. R. Richmond, and G. A. Trafton. 1963. Distribution of cesium-137 in mice and dogs after chronic exposure. In *Annual report of Health Division*, LAMS-3034, pp. 41-47. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Furchner, J. E., et al. 1965. Effect of conditioning to temperature stress on the excretion of cesium by mice. In *Annual report of Health Division*, LA-3432-MS, pp. 33-35. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Gallegos, A. F. and F. W. Whicker. 1971. Radiocesium retention by rainbow trout as affected by temperature and weight. In *Radionuclides in ecosystems*, ed. D. J. Nelson, CONF-710501-P1, pp. 361-71. Proceedings of the 3d national symposium on radioecology held in Oak Ridge, Tenn., May 10-12, 1971. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Goldman, M. and L. K. Bustad, eds. 1972. *Biomedical implications of radiostrontium exposure*, CONF-710201. Proceedings of a symposium held in Davis, Calif., February 22-24, 1971. Springfield, Va.: National Technical Information Service.
- Goldman, M. and R. J. Della Rosa. 1967. Studies on the dynamics of strontium metabolism under conditions of continual ingestion to maturity. In Lenihan, Loutit, and Martin 1967, pp. 181-94.
- Goss, J. A. and E. M. Romney. 1957. *Effects of bicarbonate and other anions on the uptake of ^{32}P , ^{45}Ca , ^{59}Fe , ^{86}Rb , ^{90}Sr , ^{106}Ru , ^{137}Cs and ^{144}Ce by bean and barley plants*. AEC report UCLA-398. Univ. of Calif. at Los Angeles.
- Greenberg, D. M. and F. M. Troeschler. 1942. Study with radioactive isotopes of excretion of calcium and strontium by way of the bile. *Proc. Soc. Exp. Biol. Med.* 49:488-91.
- Greig, W. R., J. F. B. Smith, J. S. Orr, and C. J. Foster. 1970. Comparative survivals of rat thyroid cells *in vivo* after ^{131}I , ^{125}I and x irradiations. *Br. J. Radiol.* 43:542-48.
- Gusmano, E. A., J. N. Concannon, S. R. Bozzo, and S. H. Cohn. 1968. Evaluation of the parameters of strontium metabolism in the rat as a function of age. *Radiat. Res.* 33:540-53.
- Hansard, S. L. 1953. A metabolism unit designed for radioisotope balance studies with dogs. *Science* 117:301-2.
- Hansard, S. L. 1969. Transplacental movement and maternal-fetal organ accretion rates of selected radiominerals in gravid cattle, sheep, and swine. In *Radiation biology of the fetal and juvenile mammal*, eds. M. R. Sikov and D. D. Mahlum, CONF-690501, pp. 9-23. Proceedings of the 9th annual Hanford biology symposium held in Richland, Wash., May 5-8, 1969. Springfield, Va.: National Technical Information Service.
- Hanson, R. O., R. D. Vidal, and P. R. Stout. 1960. Radioisotopes in soils: Physical-chemical composition. In Caldecott and Snyder 1960, pp. 23-36.
- Hanson, W. C. 1980. *Transuranium elements in the environment*. DOE/TIC-22800. Springfield, Va.: National Technical Information Service.
- Harrison, G. E., W. H. A. Raymond, and H. C. Tretheway. 1955. The metabolism of strontium in man. *Clin. Sci.* 14:681-95.
- Häsänen, E., S. Kolehmainen, and J. K. Miettinen. 1967. Biological half-time of ^{137}Cs in three species of fresh-water fish: Perch, roach and rainbow trout. In Åberg and Hungate 1967, pp. 921-24.
- Hinners, R. A. 1957. [USN Radiological Defense Laboratory.] Paper in *J. Am. Soc. Naval Engineers*, August 1957.
- Hoss, D. E. and John P. Baptist. 1971. Accumulation of soluble and particulate radionuclides by estuarine fish. In *Radionuclides in ecosystems*, ed. D. J. Nelson, CONF-710501, pp. 776-82. Proceedings of the 3d national symposium on radioecology held in Oak Ridge, Tenn., May 10-12, 1971. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Hungate, F. P., R. L. Uhler, and J. F. Cline. 1958. Radiostrontium uptake by plants. *Hanford biology research annual report for 1957*. HW-53500, pp. 7-17. Richland, Wash.: Hanford Works.
- IAEA. See International Atomic Energy Agency.
- ICRP. See International Commission on Radiological Protection.

- International Atomic Energy Agency. 1976. *Effects of ionizing radiation on aquatic organisms and ecosystems*, Technical report series no. 172, p. 131. Vienna.
- International Commission on Radiological Protection. 1973. *Alkaline earth metabolism in adult man*. ICRP publ. 20, p. 92. Oxford-New York: Pergamon Press. Also *Health Phys.* 24:125-221.
- James, R. H., D. N. McNelis, E. L. Whittaker, and N. C. Kennedy. 1970. *Aerosol preparation, generation, and assessment Project Hare*. SWRHL-75-r, Las Vegas: Southwestern Radiological Health Laboratory.
- Kahn, B., C. P. Straub, P. J. Robbins, H. N. Wellman, R. A. Seltzer, and N. C. Telles. 1969. Retention of radiostrontium, strontium, calcium, and phosphorus by infants. *Pediatrics* 43(4), pt. 2 (Suppl.):651-731.
- Kamb, B. and L. Pauling. 1959. The effects of strontium-90 on mice. *Proc. Natl. Acad. Sci.* 45:54-69. See also U.S. Congressional hearings 1959 (chapter 12) 3:2347-62.
- Keppel, H. 1969. Morphological, physiological, and environmental conditions affecting the accumulation of long-lived radionuclides from fission products by plants. In *Environmental contamination by radioactive materials*, pp. 99-111. Proceedings of a symposium held in Vienna, March 24-28, 1969. Vienna: International Atomic Energy Agency.
- Kirchmann, R., E. Fagnjart, and S. Van Puymbroeck. 1967. Studies on foliar contamination by radiocaesium and radiostrontium. In Åberg and Hungate 1967, pp. 475-83.
- Klassovskii, I. A., I. Vasilenko, and N. F. Terekhov. 1970. Methods and results of evaluation of an equivalent dose of radiation to the thyroid gland in irradiation of experimental animals and man with radioisotopes of iodine or mixtures thereof. In *Radio-biologicheskii eksperiment i Chelovek*, ed. Yu. I. Moskalev. National Institutes of Health translation NIH-71-219 (1971).
- Klepper, B. and D. K. Craig. 1974. Foliar deposition of plutonium aerosols. In *Pacific Northwest Laboratory annual report for 1974 to the USAEC Division of Biomedical and Environmental Sciences, Part 2 Ecological Sciences*. BNWL-1950, pt. 2, Ecological Sciences, pp. 50-52. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Knizhnikov, V. A. and A. N. Marei. 1967. Strontium metabolism in man. In Lenihan, Loutit, and Martin 1967, pp. 71-82.
- Kornberg, H. A. 1960. Radioisotopes and environmental circumstances: The passage of pairs of elements through food chains. In Caldecott and Snyder 1960, pp. 255-68.
- Krumholz, L. A. and R. F. Foster. 1957. Accumulation and retention of radioactivity from fission products and other radiomaterials in fresh-water organisms. Chapter 9 in NAS-NRC 1957, pp. 88-95.
- Krumholz, L. A., E. D. Goldberg, and H. Boroughs. 1957. Ecological factors involved in the uptake, accumulation, and loss of radionuclides by aquatic organisms. Chapter 7 in NAS-NRC 1957, pp. 69-79.
- Lange, A. H., W. L. Ehrler, and C. Hamner. 1955. *The effect of certain environmental factors on mineral uptake by bean plants. II. Calcium and strontium uptake*. AEC report UCLA-331. Univ. of Calif. at Los Angeles.
- Langham, W. H. 1965. Considerations of biospheric contamination by radioactive fallout. In Fowler 1965, pp. 3-18.
- Langham, W. H. and E. C. Anderson. 1959. Cs¹³⁷ biospheric contamination from nuclear weapons tests. *Health Phys.* 2:30-48.
- L'Annunziata, M. F. and J. O. Legg, eds. 1984. *Isotopes and radiation in agricultural sciences*. Vol. 1, *Soil-plant-water relationships*; vol. 2 *Animals, plants, food and environment*. New York: Academic Press.
- Laszlo, D. and H. Spencer. 1959. Radiostrontium metabolism and decontamination in man; chelation in biology and medicine. In *Proceedings of the 2d United Nations international conference on the peaceful uses of atomic energy*, vol. 23, pp. 425-33. Held in Geneva, September 1-13, 1958. Geneva: United Nations. [Also in (with co-authors) *Progress in nuclear energy*, vol. 2, Medical Sciences, pp. 151-68. New York-London: Pergamon Press.]

- Lee, W., R. P. Chiacchierini, B. Shleien, and N. C. Telles. 1982. Thyroid tumors following ^{131}I or localized x irradiation to the thyroid and pituitary glands in rats. *Radiat. Res.* 92:307-19.
- Lenihan, J. M. A. 1967. Studies in strontium metabolism. I. Correlation of strontium-90 levels in foetal bone and maternal diet. In Lenihan, Loutit, and Martin 1967, pp. 57-61.
- Lenihan, J. M. A., J. F. Loutit, and J. H. Martin, eds. 1967. *Strontium metabolism*. Proceedings of an international symposium held in Chapelcross, Glasgow and Strontian, Scotland, May 5-7, 1966. London-New York: Academic Press.
- Lindsay, S., G. D. Potter, and I. L. Chaikoff. 1957. Thyroid neoplasms in the rat: A comparison of naturally occurring and iodine-131-induced tumors. *Cancer Res.* 17:183-89.
- Lindsay, S., G. E. Sheline, G. D. Potter, and I. L. Chaikoff. 1961. Induction of neoplasms in the thyroid gland of the rat by x-irradiation of the gland. *Cancer Res.* 21:9-16.
- Liniecki, J. 1967. Chronic accumulation of strontium-90 in the body as predicted from the retention of a single tracer dose. In Lenihan, Loutit, and Martin 1967, pp. 83-91.
- Lotz, W. E., J. C. Gallimore, and G. A. Boyd. 1952. How to get good gross autoradiographs of large undecalcified bones. *Nucleonics* 10(3):28-31.
- Lotz, W. E. and P. M. Johnston. 1953. Preparation of microautoradiographs with the use of stripping film. *Nucleonics* 11(3):54.
- Lough, S. A., J. Rivera, and C. L. Comar. 1963. Retention of strontium, calcium, and phosphorus in human infants. *Proc. Soc. Exp. Biol. Med.* 112:631-36.
- Marcus, C. S. and R. H. Wasserman. 1965. Comparison of intestinal discrimination between calcium 47, strontium 85, and barium 133. *Am. J. Physiol.* 209:973-77.
- Martin, D. C. 1954. *The absorption and translocation of radiostrontium by the leaves, fruits and roots of certain vegetable plants*. Ph.D. Thesis, Mich. State Univ. [Quoted in NAS-NRC 1957.]
- Mason, D. J., S. C. Black, and D. S. Barth. 1971. ^{131}I dairy cow uptake studies using a submicrometer synthetic dry aerosol (Project SIP). SWRHL-39-r. Las Vegas: Southwestern Radiological Health Laboratory.
- Merten, D. and W. Buchheim. 1967. Fixation of radioactive material as influenced by the microstructure of the plant surface. In Åberg and Hungate 1967, pp. 485-88.
- McClellan, R. O. and R. K. Jones. 1969. ^{90}Sr -induced neoplasia: A selective review. In *Delayed effects of bone-seeking radionuclides*, eds. C. W. Mays, W. S. S. Jee, R. D. Lloyd, B. J. Stover, J. H. Dougherty, and G. N. Taylor, pp. 293-322. Salt Lake City: Univ. of Utah Press.
- McClellan, R. O., L. K. Bustad, W. J. Clarke, N. L. Dockum, J. R. McKenney, and H. A. Kornberg. 1962. Bone-seeking radionuclides in miniature swine. In *Some aspects of internal irradiation*, eds. T. F. Dougherty, W. S. S. Jee, C. W. Mays, and B. J. Stover, pp. 341-48. Proceedings of a symposium held at Heber, Utah, May 8-11, 1961. New York-Oxford: Pergamon Press.
- McClellan, R. O., W. J. Clarke, H. A. Ragan, D. N. Wood, and L. K. Bustad. 1963. Comparative effects of ^{131}I and x-irradiation on sheep thyroids. *Health Phys.* 9:1363-68.
- Menzel, R. G. 1954. Competitive uptake by plants of potassium, rubidium, cesium, and calcium, strontium, barium from soils. *Soil Sci.* 77:419-25.
- Menzel, R. G. 1960. Radioisotopes in soils: Effects of amendments on availability. In Caldecott and Snyder 1960, pp. 37-46.
- Menzel, R. G. 1967. Airborne radionuclides and plants. In *Agriculture and the quality of our environment*, ed. N. C. Brady, pp. 57-75. Washington, D.C.: American Association of Advanced Science.
- Middleton, L. J. 1960. Radioisotopes in plants: Practical aspects of aerial contamination with strontium⁸⁹ and cesium¹³⁷. In Caldecott and Snyder 1960, pp. 86-96.
- Milbourn, G. M., F. B. Ellis, and R. S. Russell. 1959. The absorption of radioactive strontium by plants under field conditions in the United Kingdom. *J. Nuclear Energy, Part A, Reactor Sci.* 10:116-32.
- Miller, C. F. 1967. The retention by foliage of silicate particles ejected from the Volcano Irazú in Costa Rica. In Åberg and Hungate 1967, pp. 501-25.

- Mraz, F. R. 1966. Development of embryos and chicks administered high levels of ^{90}Sr - ^{90}Y . In *Proceedings of the 7th international congress of nutrition*, vol. 5, pp. 841-45. Held at Hamburg 1966. Braunschweig, West Germany: Verlag Fiedr. Vieweg and Sohn.
- Mraz, F. R. 1969. Toxicity of high levels of zinc-65 to avian embryos. *Poult. Sci.* 48:1460-62.
- Mraz, F. R. 1970. Embryonic uptake of ^{45}Ca and ^{89}Sr . *Poult. Sci.* 49:310-11.
- Mraz, F. R. and H. Patrick. 1957. Influence of dietary potassium on potassium-42, rubidium-86 and cesium-134 retention in the rat. *Proc. Soc. Exp. Biol. Med.* 96:497-99.
- Mraz, F. R., P. L. Wright, and T. M. Ferguson. 1964. Toxicity of high levels of calcium-45, strontium-90 and promethium-147 to avian embryos. *Proc. Soc. Exp. Biol. Med.* 116:1114-18.
- Mraz, F. R., P. L. Wright, and T. M. Ferguson. 1967. Effect of dietary strontium on reproductive performance of the laying hen. In Lenihan, Loutit, and Martin 1967, pp. 247-53.
- Müller, J. and eight contributors. 1970. Effects of chronic irradiation and evaluation of the risk from incorporated ^{90}Sr and ^{226}Ra in man. *Medica Monographia* 45. Prague, Czechoslovakia: Acta Universitatis Carolinae Medica.
- Müller, J., A. David, M. Rejskova, D. Brezikova. 1961. Chronic occupational exposure to strontium-90 and radium-226. *Lancet* 2:129-31.
- Murphy, C. E., Jr. and J. C. Corey. 1976. Absorption of tritiated water vapor from the atmosphere by the needles of pine trees. In *Radioecology and energy resources*, ed. C. E. Cushing, Ecological Society of America special publ. no. 1, pp. 108-12. Proceedings of the 4th national symposium on radioecology held at Oreg. State Univ., May 12-14, 1975. Stroudsburg, Pa.: Dowden, Hutchinson & Ross, Inc.
- Nakatani, R. E. 1966. Biological response of rainbow trout (*Salmo gairdneri*) ingesting zinc-65. In *Disposal of radioactive wastes into seas, oceans, and surface waters*. Proceedings of a symposium held in Vienna, May 16-20, 1966. Vienna: International Atomic Energy Agency.
- Nakatani, R. E. and R. F. Foster. 1963. Effect of chronic feeding of Sr^{90} - Y^{90} on rainbow trout. In *Radioecology*, eds. V. Schultz and A. W. Klement, Jr., pp. 359-62. Proceedings of the 1st national symposium on radioecology held at Colo. State Univ., September 10-15, 1961. New York: Reinhold Publishing Company; Washington, D.C.: American Institute of Biological Sciences.
- NAS-NRC. See National Academy of Sciences-National Research Council.
- National Academy of Sciences-National Research Council. 1957. *The effects of atomic radiation on oceanography and fisheries*. Report of a NAS committee, NAS-NRC publ. 551. Washington, D.C.
- National Academy of Sciences-National Research Council. 1963. *The behavior of radioactive fallout in soils and plants*. Review prepared for the committee on effects of atomic radiation on agriculture and food supplies of the U.S. NAS-NRC publ. 1092. Washington, D.C.
- National Council on Radiation Protection and Measurements. 1977. Cesium-137 from the environment to man: Metabolism and dose. NCRP report no. 52. Bethesda, Md.
- National Council on Radiation Protection and Measurements. 1978. *Physical, chemical, and biological properties of radiocerium relevant to radiation protection guidelines*. NCRP report no. 60. Bethesda, Md.
- National Council on Radiation Protection and Measurements. 1985. *Induction of thyroid cancer by ionizing radiation*. NCRP report no. 80. Bethesda, Md.
- Naval Radiological Defense Laboratory. 1968. *USNRDL technical program summary for FY 1969*. NRDL-PR-68-17.
- Nay, U. 1967. The adsorption of fall-out ^{90}Sr at the surface of different grass species. In Åberg and Hungate 1967, pp. 489-500.
- NCRP. See National Council on Radiation Protection and Measurements.
- Neel, J. W., et al. 1953. *Soil/plant interrelationships with respect to the uptake of fission products. I. The uptake of ^{90}Sr , ^{137}Cs , ^{106}Ru , ^{144}Ce , and ^{91}Y* . AEC report UCLA-247. Univ. of Calif. at Los Angeles.

- Nelson, D. J. 1967. The prediction of ^{90}Sr uptake in fish using data on specific activities and biological half lives. In Åberg and Hungate 1967, pp. 843-51.
- Nishita, H., R. Kowalewsky, and K. Larson. 1954. Fixation and extractability of fission products contaminating various soils and clays. I. Strontium-89, strontium-90, yttrium-91, ruthenium-106, cesium-131, and cesium-144. AEC report UCLA-282. Univ. of Calif. at Los Angeles.
- Nishita, H. and K. H. Larson. 1957. Summary of certain trends in soil-plant relationship studies and the biological availability of fallout debris. AEC report UCLA-401. Univ. of Calif. at Los Angeles.
- Nishita, H., E. M. Romney, and K. H. Larson. 1965. Uptake of radioactive fission products by plants. In Fowler 1965, pp. 55-81.
- Nishita, H., E. M. Romney, G. V. Alexander, and K. H. Larson. 1959 and 1960. Influence of K and Cs on the release of Cs 137 from three soils. AEC report UCLA-437, and Soil Sci. 89:167-76. [See also Soil Sci. 94:187-97 (1962).]
- Norris, W. P. and W. Kisielski. 1948. Comparative metabolism of radium, strontium and calcium. In *Biological applications of tracer elements*, vol. 13, pp. 164-72. Proceedings on a symposium on quantitative biology held in Cold Spring Harbor, N.Y. Long Island, N.Y.: The Biological Laboratory.
- NRDL. See Naval Radiological Defense Laboratory.
- OPNAV. 1959. *History of the United States Naval Radiological Defense Laboratory*. OPNAV Report 5750-5. [Covers the period 1946-1958.]
- Olson, P. R. 1971. Accumulation of calcium-45 in developing Coho salmon eggs and fry reared in varying concentrations of stable calcium. In *Radionuclides in ecosystems*, ed. D. J. Nelson, CONF-710501-P2, pp. 866-74. Proceedings of the 3d national symposium on radioecology held in Oak Ridge, Tenn., May 10-12, 1971. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Ophel, I. L. and J. M. Judd. 1967. Experimental studies of radiostrontium accumulation by freshwater fish from food and water. In Åberg and Hungate 1967, pp. 859-65.
- Palmer, R. F. and R. C. Thompson. 1961. Discrimination in intestinal absorption of strontium and calcium. *Proc. Soc. Exp. Biol. Med.* 108:296-300.
- Palmer, R. F., R. C. Thompson, and H. A. Kornberg. 1958. Effect of calcium on deposition of strontium-90 and calcium-45 in rats. *Science* 127:1505-06.
- Pecher, C. and J. Pecher. 1941. Radiocalcium and radio-strontium metabolism in pregnant mice. *Proc. Soc. Exp. Biol. Med.* 46:91-94.
- Pediatrics. 1968. Conference on the pediatric significance of peacetime radioactive fallout. *Pediatrics* 41(1), pt. 2 (Suppl.):167-378.
- PHS. See Public Health Service.
- Polikarpov, G. G. 1967. Regularities of uptake and accumulation of radionuclides in aquatic organisms. In Åberg and Hungate 1967, pp. 819-25.
- Polikarpov, G. G., Yu. P. Zaitsev, G. V. Barinov, and V. P. Parchevsky. 1967. General features of the concentration processes of radioactive substances by hydrobionts in different seas of the world ocean. In Åberg and Hungate 1967, pp. 771-90.
- Poole, C. M., W. P. Norris, and T. E. Fritz. 1968. Cesium-137: Current status and late effects. In *Annual report of the Biological and Medical Research Division*. ANL-7535. Argonne, Ill.: Argonne National Laboratory.
- Price, K. R. 1972. Uptake of ^{237}Np , ^{239}Pu , ^{241}Am , and ^{244}Cm from soil by tumbleweed and cheatgrass. BNWL-1688. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Price, K. R. 1973. Tumbleweed and cheatgrass uptake of transuranium elements applied to soil as organic acid complexes. BNWL-1755. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Prosser, C. L., D. W. Hagen Jr., and W. Grundhauser. 1947. The lethal action of x-radiation, stable elements of fission elements, Sr^{89} and (Ba-La) 140 on goldfish. AEC report MDDC-1480, declassified November 20, 1947.

- Prosser, C. L., W. Pervinsek, J. Arnold, G. Svihla, and P. C. Thompkins. 1945. *Accumulation and distribution of radioactive strontium, barium-lanthanum, fission mixture and sodium in goldfish*. AEC report MDDC-496, pp. 1-39.
- Public Health Service. 1965-1966. *Radiological health research*. Summary report July 1965-December 1966. Publication no. 1672. Washington, D.C.
- Public Health Service. 1967. *Radiation bio-effects*. Summary report from the National Center for Radiological Health, pp. 2-3 and 25-31. Washington, D.C.
- Public Health Service. 1968. *Radiation bio-effects*. Summary report from the Bureau of Radiological Health, pp. 59-81. Washington, D.C.
- Public Health Service. 1970. *Radiation bio-effects*. Summary report January-December 1970 for Bureau of Radiological Health. BRH/DBE 70-77. Washington, D.C.
- Rediske, J. H., J. F. Cline, and A. A. Selders. 1955a. The absorption of fission products by plants. *Biology research annual report 1954*. HW-35917, pp. 40-46. Richland, Wash.: Hanford Works.
- Rediske, J. H., J. F. Cline, and A. A. Selders. 1955b. *The absorption of fission products by plants*. HW-36734. Richland, Wash.: Hanford Atomic Products Operation.
- Rediske, J. H. and F. P. Hungate. 1956. The absorption of fission products by plants. In *Proceedings of the international conference on the peaceful uses of atomic energy*, vol. 13, pp. 354-56. Held in Geneva, August 8-20, 1955. New York: United Nations.
- Rediske, J. H. and A. A. Selders. 1952. The absorption and translocation of several fission products by plants. In *Biology research annual report 1951*. HW-25021, pp. 118-25. Richland, Wash.: Hanford Works. [See also *Plant Physiol.* 28:594-605 (1953).]
- Rice, T. R. and J. P. Baptist. 1974. Ecologic effects of radioactive emissions from nuclear power plants. In *Human and ecologic effects of nuclear power plants*, ed. L. A. Sagan, pp. 373-439. Springfield, Ill.: Charles Thomas.
- Richmond, C. R., J. E. Furchner, and W. H. Langham. 1962. Long-term retention of radiocesium by man. *Health Phys.* 8:201-5.
- Richmond, C. R. and J. E. London. 1967. Long-term retention of cobalt-60 by rats. In *Annual report of Health Division*. LA-3848-MS, pp. 84-86. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Richmond, C. R., J. E. London, and J. E. Furchner. 1964. Metabolism of radiocesium by man and selected laboratory mammals. *Radiat. Res.* 22:226-27.
- Richmond, C. R., J. E. Furchner, P. N. Dean, and P. McWilliams. 1964. Electronic processing and analysis of metabolic data. *Health Phys.* 10:3-13.
- Rivera, J. 1967. Predicting strontium-90 concentrations in human bone. In Lenihan, Loutit, and Martin 1967, pp. 47-55.
- Roberts, H., Jr. and R. G. Menzel. 1965. Availability of exchangeable and nonexchangeable strontium-90 to plants. In Fowler 1965, pp. 21-29.
- Romney, E. M. and J. D. Childress. 1961. *Reaction of tungsten in soils and its uptake by plants*. AEC report UCLA-494. Univ. of Calif. at Los Angeles.
- Romney, E. M., G. V. Alexander, H. Nishita, and K. H. Larson. 1960. *Influence of calcium and strontium amendments on strontium-90 uptake by Ladino Clover upon prolonged cropping*. AEC report UCLA-462. Univ. of Calif. at Los Angeles. Also *Soil Sci. Soc. Am. Proc.* 25:299-301 (1961).
- Romney, E. M., G. V. Alexander, W. A. Rhoads, and K. H. Larson. 1959. Influence of calcium on plant uptake of Sr 90 and stable strontium. *Soil Sci.* 87:160-65.
- Romney, E. M., et al. 1956. *Effects of calcium and strontium on plant uptake of strontium-90 and stable strontium from nutrient solutions in soils*. AEC report UCLA-374. Univ. of Calif. at Los Angeles.
- Romney, E. M., J. W. Neel, H. Nishita, J. H. Olafson, and K. H. Larson. 1957. Plant uptake of Sr90, Y91, Ru106, Cs137, and Ce144 from soils. *Soil Sci.* 83:369-76.
- Rosoff, B., S. H. Cohn, and H. Spencer. 1963. 1. Cesium-137 metabolism in man. *Radiat. Res.* 19:643-54.
- Rundo, J. 1967. Kinetics of strontium-85 deposition in the skeleton during chronic exposure. In Lenihan, Loutit, and Martin 1967, pp. 131-38.

- Russell, R. S. 1960. Radioisotopes and environmental circumstances: The passage of fission products through food chains. In Caldecott and Snyder 1960, pp. 269-92.
- Saenger, E. L., R. A. Seltzer, T. D. Sterling, and J. G. Kereiakes. 1963. Carcinogenic effects of ^{131}I compared with x-irradiation—A review. *Health Phys.* 9:1371-84.
- Sanders, C. L., R. A. Gelman, and A. W. Conklin. 1981. Pulmonary toxicity of Mount St. Helens volcanic ash. In *Annual report for 1980 to the DOE Assistant Secretary for Environment, Part 1 Biomedical sciences*, PNL-3700, pt. 1, pp. 20-21. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Schachter, D. and S. M. Rosen. 1959. Active transport of Ca^{45} by the small intestine and its dependence on vitamin D. *Am. J. Physiol.* 196:357-62.
- Schreckhise, R. G. and J. F. Cline. 1980. Comparative uptake and distribution of plutonium, americium, curium, and neptunium in four plant species. In Hanson 1980, pp. 361-80.
- Schults, D. W. and K. W. Malueg. 1971. Uptake of radiophosphorus by rooted aquatic plants. In *Radionuclides in ecosystems*, ed. D. J. Nelson, CONF-710501-P1, pp. 417-24. Proceedings of the 3d national symposium on radioecology held in Oak Ridge, Tenn., May 10-12, 1971. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Seymour, A. H. and V. A. Nelson. 1971. Biological half-lives for zinc and mercury in the Pacific Oyster (*Crassostrea gigas*). In *Radionuclides in ecosystems*, ed. D. J. Nelson, CONF-710501-P2, pp. 849-56. Proceedings of the 3d national symposium on radioecology held in Oak Ridge, Tenn., May 10-12, 1971. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Shimmins, J., D. A. Smith, B. E. C. Nordin, and L. Burkinshaw. 1967. A comparison between calcium-45 and strontium-85 absorption, excretion and skeletal uptake. In Lenihan, Loutit, and Martin 1967, pp. 149-59.
- Sparrow, A. H. and H. J. Evans. 1961. *Nuclear factors affecting radiosensitivity. I. The influence of nuclear size and structure, chromosome complement and DNA content.* BNL-675, pp. 76-100. Upton, N.Y.: Brookhaven National Laboratory.
- Sparrow, A. H. and J. P. Miksche. 1961. Correlation of nuclear volume and DNA content with higher plant tolerance to chronic radiation. *Science* 134:282-83.
- Sparrow, A. H. and G. M. Woodwell. 1963. Prediction of sensitivity of plants to chronic gamma irradiation. In *Radioecology*, eds. V. Schultz and A. W. Klement, Jr., pp. 257-70. Proceedings of the 1st national symposium on radioecology held at Colo. State Univ., September 10-15, 1961. New York: Reinhold Publishing Corporation; Washington, D.C.: American Institute of Biological Sciences. [Note: contains many references to earlier work.]
- Sparrow, A. H., R. C. Sparrow, K. H. Thompson, L. A. Schairer. 1965. The use of nuclear and chromosomal variables in determining and predicting radiosensitivities. In *The use of induced mutations in plant breeding. Radiation botany*, suppl. 5:101-32.
- Spencer, H., L. Kramer, and J. Samachson. 1972. Metabolism and removal of radiostrontium in man. In Goldman and Bustad 1972, pp. 31-48.
- Spencer, H., D. Laszlo, and M. Brothers. 1957. Strontium⁸⁵ and Calcium⁴⁵ metabolism in man. *J. Clin. Invest.* 36:680-88.
- Spencer, H., B. Rosoff, A. Feldstein, S. H. Cohn, and E. A. Gusmano. 1965. Metabolism of zinc-65 in man. *Radiat. Res.* 24:432-45.
- Spencer, H., J. Samachson, E. P. Hardy, Jr., and J. Rivera. 1967. Effect of low and high calcium intake on Sr^{90} metabolism in adult man. *Int. J. Appl. Radiat. Isot.* 18:605-14.
- Spencer, H., J. Samachson, E. P. Hardy, Jr., and J. Rivera. 1972. Effect of orally and intravenously administered stable strontium on ^{90}Sr metabolism in man. *Radiat. Res.* 51:190-203.
- Spencer, H., J. Samachson, B. Kabakow, and D. Laszlo. 1958. Factors modifying radiostrontium excretion in man. *Clin. Sci.* 17:291-301.
- Stanley, R. E., S. C. Black, and D. S. Barth. 1969. *^{131}I dairy cow studies using a dry aerosol (Project Alfalfa).* SWRHL-42-r. Las Vegas: Southwestern Radiological Health Laboratory.

- Taylor, D. M. 1967. The role of oxidative phosphorylation in calcium and strontium absorption from the gastro-intestinal tract. In Lenihan, Loutit, and Martin 1967, pp. 175-79.
- Terec, T. M., E. A. Gusmano, and S. H. Cohn. 1965. Decrement in radiostrontium retention following stable strontium prefeeding in the growing rat. *J. Nutr.* 87:399-406.
- Thompson, R. C. 1960. Radioisotope absorption and methods of elimination: Nutritional considerations. In Caldecott and Snyder 1960, pp. 514-25.
- Thompson, R. C. and P. L. Hackett. 1967. Urinary/fecal excretion ratios of strontium and calcium in the rat. In Lenihan, Loutit, and Martin 1967, pp. 255-60.
- Townsley, S. J. 1967. The concentration of ^{90}Sr and other nuclides of strontium in fish. In Åberg and Hungate 1967, pp. 867-78.
- Tyler, S. A., N. D. Kretz, and W. P. Norris. 1969. Dependence of ^{137}Cs retention on age in the fetal and juvenile beagle dog. In *Radiation biology of the fetal and juvenile mammal*, eds. M. R. Sikov and D. D. Mahlum, CONF-690501, pp. 191-205. Proceedings of the 9th annual Hanford biology symposium held in Richland, Wash., May 5-8, 1969. Springfield, Va.: National Technical Information Service.
- Uhler, R. L. 1959. Influence of calcium on Sr^{90} uptake. *Hanford biology annual report for 1958*. HW-59500, pp. 33-40. Richland, Wash.: Hanford Works.
- United Nations Scientific Committee on the Effects of Atomic Radiation. 1977. *Ionizing radiation: Sources and biological effects*. Supplement 40 (A/32/40), pp. 121-38 and 141-46. Report to the General Assembly, 32d sess. New York: United Nations.
- United Nations Scientific Committee on the Effects of Atomic Radiation. 1982. *Ionizing radiation: Sources and biological effects*. Supplement 45 (A/37/45), pp. 217-19 and 220-22. Report to the General Assembly, 37th sess. New York: United Nations.
- UNSCEAR. See United Nations Scientific Committee on the Effects of Atomic Radiation.
- Van der Borcht, O. and S. Van Puymbroeck. 1967. Ionic regulation and radiocontamination: "Active transport" of alkaline earth ions in freshwater gastropods (Mollusca). In Åberg and Hungate 1967, pp. 925-30.
- Vaughan, B. E. 1974. Foreword in *Pacific Northwest Laboratory annual report for 1974 to the ERDA Division of Biomedical and Environmental Research, Part 2 Ecological Sciences*. BNWL-1950, pt. 2, pp. iii-v. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Walinder, G. 1972. Late effects of irradiation on the thyroid gland in mice, I. Irradiation of adult mice. *Acta Radiol. Ther. Phys. Biol.* 11:433-51.
- Walinder, G., C.-J. Jönsson, and A.-M. Sjöden. 1972. Dose rate dependence in the goitrogen-stimulated mouse thyroid: A comparative investigation of the effects of roentgen, ^{131}I and ^{132}I irradiation. *Acta Radiol. Ther. Phys. Biol.* 11:24-36.
- Walinder, G. and A.-M. Sjöden. 1971. Effect of irradiation on thyroid growth in mouse foetuses and goitrogen challenged adult mice. *Acta Radiol. Ther. Phys. Biol.* 10:579-92.
- Wallace, A., E. M. Romney, R. T. Mueller, and P. M. Patel. 1976. ^{241}Am availability to plants influenced by chelating agents. In *Radioecology and energy resources*, ed. C. E. Cushing, Jr., Ecological Society of American special publ. no. 1, pp. 104-7. Proceedings of the 4th national symposium on radioecology held at Oregon State Univ., May 12-14, 1975, Stroudsburg, Pa.: Dowden, Hutchinson & Ross, Inc.
- Walser, M. and B. H. B. Robinson. 1963. Renal excretion and trabecular reabsorption of calcium and strontium. In *The transfer of calcium and strontium across biological membranes*, ed. R. H. Wasserman, pp. 305-26. New York: Academic Press.
- Ward, J. M. and J. F. Wright. 1972. Pathology of radiostrontium exposure in cats. *Radiat. Res.* 51:84-96.
- Ward, J. M., J. F. Wright, N. S. Nelson, E. Berman, C. G. Liddle, and A. Hellman. 1972. Bone and soft-tissue neoplasms in cats exposed to radiostrontium. *J. Nat. Cancer Inst.* 48:1543-46.
- Wasserman, R. H. 1960. Radioisotope absorption and methods of elimination: A critical review. In Caldecott and Snyder 1960, pp. 564-73.
- Wasserman, R. H. and C. L. Comar. 1961. *Annotated bibliography of strontium and calcium metabolism in man and animals*. Miscellaneous publ. no. 821, January 1961. Washington, D.C.: U.S. Department of Agriculture, Agricultural Research Service.

- Wasserman, R. H., F. A. Kallfelz, and C. L. Comar. 1961. Active transport of calcium by rat duodenum in vivo. *Science* 133:883-84.
- Wasserman, R. H., F. W. Lengemann, and C. L. Comar. 1958. Comparative metabolism of calcium and strontium in lactation. *J. Dairy Sci.* 41:812-21.
- Wasserman, R. H., C. L. Comar, N. M. Nold, and F. W. Lengemann. 1957. Placental transfer of calcium and strontium in the rat and rabbit. *Am. J. Physiol.* 189:91-97.
- Wasserman, R. H., F. W. Lengemann, J. C. Thompson, Jr., and C. L. Comar. 1965. The transfer of fall-out radionuclides from diet to man. In Fowler 1965, pp. 204-44.
- Watson, D. G., L. A. George, and P. L. Hackett. 1959. Effects of chronic feeding of phosphorus-32 on rainbow trout. In *Hanford biology research annual report for 1958*. HW-59500, p. 73. Richland, Wash.: Hanford Atomic Products Operation.
- Watters, R. L., D. N. Edgington, T. E. Hakonson, W. C. Hanson, M. H. Smith, F. W. Whicker, and R. E. Wildung. 1980. Synthesis of the research literature. In Hanson 1980, pp. 1-44.
- Wildung, R. E. and T. R. Garland. 1980. The relationship of microbial processes to the fate and behavior of transuranic elements in soil, plants, and animals. In Hanson 1980, pp. 300-335.
- Woodward, K. T., C. R. Richmond, and W. Langham. 1956. Measurement of retention and excretion of radioisotopes of the alkali metals by mice and rats, using an annular liquid scintillation counter. In *Proceedings of the Health Physics Society*, held June 1956, pp. 79-88.
- Woodwell, G. M. and A. H. Sparrow. 1965. Effects of ionizing radiation of ecological systems. In *Ecological effects of nuclear war*. BNL-917, pp. 20-38. Upton, N.Y.: Brookhaven National Laboratory.
- Wright, P. L. and F. R. Mraz. 1965. Toxicity of sulfur-35, selenium, and tellurium to avian embryos. *Proc. Soc. Exp. Biol. Med.* 118:534-39.

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Capsule Chronology

- April 1956** Project 56 carried out in Areas 11 and 5 (GMX) of Nevada Test Site (NTS).^(a) Four "safety shots" and 22 GMX shots. Biomedical interest is environmental contamination with plutonium. Long-term study proves decrease in availability for wind resuspension with time.
- 1957** Test Group 57 of Operation Plumbbob in Area 13 of NTS. A biomedical evaluation of hazards of the one-point detonation. Indicates that cloud passage dose is larger than that from residual environmental contamination. Acute and chronic phase out to 160 days in field. Air concentration of plutonium found to fall off rapidly with time (Rochester, Sandia, military). Data used for confirming surface contamination guidelines (military).
- 1958** Fission-product-release studies at Idaho Falls (Wilson, Boecker, Lie, Smith, Thomas at Rochester; Terry, Air Force; Idaho personnel). Uses melted fuel elements from reactors.
- 1959** Static tests of nuclear rocket at NTS (Kiwi). Several laboratories and services involved, but most of the biomedical data come from Langham at Los Alamos.
- 1960** Publication of data from TG '57' (especially Wilson, Thomas, and Stannard for biomedical aspects).
- 1961** SNAP (Systems for Nuclear Auxiliary Power) first used in space program. Continues through the present and includes sources on the moon and in interplanetary space.
- Project Plowshare begins. An ambitious program under the Atoms for Peace umbrella. Twenty-seven specific shots and large computational effort concerning the feasibility for digging a new transisthmus canal with nuclear explosives. Other "geographical engineering" efforts.
- 1962** Cratering event Sedan at NTS. Part of Project Plowshare. Followed up for several years (Essington, Gerber, Martin, Turner).
- 1963** Operation Roller Coaster approved. Joint U.S.-U.K. operation at Tonopah Test Range in Nevada. Implemented subsequently as a massive investigation of the nature and fate of plutonium aerosols physically, spatially, and biologically. Four separate tests. Termed the largest inhalation experiment ever performed under field conditions.
- 1964** SNAP device (SNAP 90 A, alias Transit 5-BN-3) burns up in atmosphere and injects 17 kCi of ²³⁸Pu. No biological hazard found since nearly all remains in stratosphere (Hardy, Krey and Volchok at HASL).
- Test detection shot in Mississippi.
- 1965** Amchitka Island, Alaska tests. Project Chariot. Much interest in arctic food chains.
- 1965-1968** Publication of Roller Coaster results (Wilson, Stewart, and Terry). Marked differences in biological behavior of plutonium aerosols depending on animal species and characteristics of aerosol. Burro considered best model for humans.

(a) For abbreviations and acronyms, see Appendix D.

- 1966 Contamination incident at Palomares, Spain. Massive clean-up operation and long-term study of inhabitants and environment (Spanish authorities, AEC, and military). Despite much wind-blown plutonium, inhabitants show little accumulation.
Salt dome test in Mississippi.
- 1967 Gasbuggy test in New Mexico. Gas stimulation experiment in Project Plowshare. Tritium is principal radionuclide contaminant.
- 1967-1970 ORNL reports on calculated doses and biomedical feasibility for constructing a new transisthmus canal with nuclear explosives (Cowser, Kaye, Rohwer, Snyder, Turner).
- 1968 Contaminating incident at Thule, Greenland. Extensive study of environmental contamination with plutonium (Danish authorities, AEC, and military).
Paper by Odland on military personnel working at Palomares.
Last announced cratering event in Plowshare series.
- 1969 National Environmental Policy Act passed.
Project Rulison test in Colorado. Second gas stimulation test in Plowshare series. Becomes grounds for litigation.
- 1970 Nevada Applied Ecology Group organized at AEC Operations Office in Las Vegas. Primarily to measure and evaluate long-term contamination of NTS, also make an inventory of transuranics (Dunaway and White). Much work done by contracts: (Soil sampling: Fowler, Essington, Gilbert; transportability of plutonium in biosphere: Au, Becket, Wildung, Garland; plant-soil interactions: Romney, et al.; grazing studies: Smith, et al.; modeling: Martin, Gilbert.)
- 1971 Stated that gas stimulation technology, e.g., Rulison type, could double the recoverable natural gas resources of the U.S. (Anspaugh et al., LLL).
- 1972 First annotated bibliography on environmental aspects of plutonium (Pfuderer, Oak Ridge) under NAEI contract. Many more follow.
- 1973 Project Rio Blanco test in Colorado. Third and last gas stimulation project in Plowshare series. Despite indications of low radiation hazard from the piped gas, public and industry acceptance of the technology does not develop.

Chapter 14

Special Environmental Test Projects

Overview

This chapter reviews a series of environmentally oriented test projects carried out largely in the decades of the 1950s and 1960s that had specific objectives outside the purview of those described in connection with the production sites (chapter 11) or fallout from nuclear weapons tests (chapter 12). They addressed urgent practical problems of the day. In some, such as the "safety shots," hazard evaluation was at the core of the enterprise. In others, biomedical studies were secondary to or shared priorities with engineering tests. The total commitment in dollars was large. This type of work does not come cheaply. The commitment of manpower from the biological and medical community was only moderate, however, partly because the military and industry supplied much technological help. Both commitments were largely justified, since results from several of the tests were at variance with predictions and, indeed, could not have been obtained in any other way. In a few instances, the biomedical findings probably helped to discourage further work on the project. In others, engineering problems were never licked, or interest faded and funds dried up before they could be solved. The personnel and expertise came primarily, in the Atomic Energy Commission family, from the Hanford Laboratories, Lawrence Livermore, Los Alamos, and the University of Rochester, the University of California at Los Angeles, and Oak Ridge; the military, e.g., Kirtland Air Force Base; industry, e.g., Sandia Laboratories, Convair-Fort Worth, and many contractors for specific jobs, plus the onsite contractors such as EG&G and Reynolds Electric; and the U.S. Public Health Service, later the Environmental Protection Agency, laboratories in Las Vegas, and at the Nevada Test Site.

The chapter begins with a review of the "safety shots" concentrated in Nevada (Project 56, Test Group 57, Project Roller Coaster), whose *raison d'être* rested on the possibility of plutonium contamination from accidental detonation of the high explosive charge(s) in a nuclear weapon, i.e., the so-called "one-point detonation." Also, what we learned from the accidents at Thule, Greenland, and Palomares, Spain, is touched on. This work made important contributions to the procedures and safety for handling and storing nuclear weapons. It also changed completely the first emphasis in hazard evaluation

from long-term residence in a contaminated area to events at the time of cloud passage. Also, it was learned that the activity level underfoot at a given location is not a reliable measure of what may be found in animals or plants, because it is where the air that is transporting radionuclides has been that controls its content, not the activity on the ground at the point of measurement. It is primarily ecological factors, the chemical form of the radionuclides and other processes that control the accumulation of radionuclides in living organisms.

The next subject is long-term follow-up of plutonium and related contamination at the Nevada Test Site as carried out by the Nevada Applied Ecology Group. This enterprise was both environmental and experimental, with work farmed out to several laboratories. Details of the Nevada Applied Ecology Group soil inventorying, soil-plant interactions, animal studies, including grazing and modeling activities, are given briefly.

The fission product release studies, centered on the planned nuclear-powered aircraft and carried out at the National Reactor Test Station (now the Idaho National Engineering Laboratory) in Idaho Falls, are reviewed. These involved melting down of "green" or "aged" fuel elements and exposure of animals and plants for subsequent pharmacokinetic studies. These again turned up phenomena not predicted by laboratory work.

Project Plowshare, one of the most ambitious of the Atoms for Peace plans, receives attention from the standpoint of biomedical and radioecological experimentation—field, laboratory, and computational. Included are the enormous efforts put into evaluation of the possibilities for excavating a new interoceanic canal in Panama or Colombia using nuclear explosives, the various actual cratering experiments at the Nevada Test Site, such as Project Sedan, and the joint U.S. government-industry experiments to stimulate release of natural gas from impermeable strata, i.e., Projects Gasbuggy, Rulison, and Rio Blanco. While it is difficult to find positive and succinct statements supporting such conclusions, the biomedical data from many of these events must have contributed significantly to the abandonment of the interoceanic canal project and perhaps also to the gas stimulation project, although the data did not indicate undue hazards with the latter. In this case, it seemed to be more an abhorrence of piping gas that had been made radioactive by man, no matter how slightly, into homes and industry.

The chapter ends with brief considerations of the biomedical aspects of radioisotope generators for electricity (Project SNAP) and the nuclear powered rocket and its reactor (NERVA and Kiwi, respectively). The former project has been quite successful operationally. Health hazards, projected and real, as measured from one mishap, appear quite manageable. By contrast, the nuclear-powered rocket was viewed with suspicion and relegated to potential use only in the upper atmosphere or in space. In addition, a special test in Mississippi and the extensive environmental work done in Alaska as prelude for some tests that never occurred are described briefly.

The research data accruing from these rather extensive projects uncovered important and interesting facts that had a major impact on the planning and characteristics of future experiments, indeed whole enterprises.

I. Background

The philosophy behind these projects requires consideration. They were expensive, demanding of manpower, and complex. In the eyes of some, they diverted

resources that might better have been devoted to controlled laboratory experiments. Nevertheless, there was considerable urgency to evaluate the potential environmental contamination problems of some of the devices, and they had to be tested anyway for engineering feasibility. Decisions could not wait for the results of slow multifactorial laboratory research. Furthermore, there were strong feelings, particularly in the military and the military applications groups in the Atomic Energy Commission (AEC) and the environmental scientists, that no laboratory experiment could reproduce the conditions of the field. This is probably true. However, it can also be argued that every field release is different, and what one finds in any one test may or may not apply to other events. With expense and other demands high, including the simple fact of contamination of real estate, albeit the most isolated of deserts, it is not practical to conduct a full spectrum of such tests. Results will always be incomplete. Some of the larger projects were able to utilize a series of events with very different potential environmental impacts. Nevertheless, the conditions for each test were very carefully planned to ensure the maximum content of information pertinent to the problems at hand. Rigid constraints were enforced regarding meteorological conditions, for example, and the event did not take place unless everything met the predetermined specifications. These did indeed maximize the chances for checking out the questions posed.

Sometimes, as we will see, the projects turned up with unexpected answers and raised new questions. These were probably among the most valuable results of these field experiments. Such results would probably have been missed entirely if only laboratory experiments and data had been employed.

On balance, it must be concluded that these projects made important contributions, despite the obvious problems of such research and the need for support that, by laboratory standards, was disproportionate to the amount of information gained. They had to be done anyway for many reasons.

Support came largely from the Department of Defense (DoD) and the AEC, but there was also some international collaboration. Personnel came from AEC and DoD laboratories in about the same proportion as for the weapons tests described in chapter 12.

The events with plutonium were described by Stannard (1973) in a general review of plutonium in the environment. This included both the planned projects and the two major accidents, the one in Thule, Greenland, and the other in Palomares, Spain. We will go into considerable depth here on the organization, plans, and results of the formal test projects and consider the two contaminating accidents briefly, especially for what they contributed in the form of research findings.

II. Safety Tests for Plutonium at and Around the Nevada Test Site

A. Purpose

These projects were developed around a single potential contaminating event: the release of plutonium (or in some cases, plutonium and uranium) from a nuclear weapon in case of accidental detonation of one (or more) of its high explosive charges. Such devices are constructed so that a nuclear reaction of any magnitude is virtually impossible under such circumstances. However,

much of the plutonium and uranium content can be (and has been) released to the environment by detonation of even one of the high explosive charges.^(a)

An elaborate protocol was set up for handling such devices to prevent accidents; but the military found it advisable also to set up guidelines for access to any areas contaminated with plutonium should such an event occur. Furthermore, teams with experience in measuring alpha-particle contamination in the environment, some of them utilizing personnel from civilian laboratories, were organized and could be brought to bear quickly in case of a "Broken Arrow" incident.

It was realized that most of the criteria employed were quite empirical and were based on scant amounts of solid information. Thus, it was decided to gather data by formal projects at the Nevada Test Site (NTS) centered first on the characteristics of the contamination (area, extent of distribution, particle size, mobility, etc.) and, later, elaborate tests of cloud behavior and uptake, distribution, retention, and possible effects of the contaminating plutonium in experimental animals.

Excellent reviews of the *raison d'être* and principal research problems involved in these projects were produced by Langham at Los Alamos (1968, 1969, 1971) after the work, which was initially done under high security restrictions, had been declassified.^(b) These reviews included general problems of plutonium contamination as well as these specific projects. Also, Langham was personally involved in both the Palomares and Thule incidents by acting as the principal biomedical consultant *in situ* for the United States. The Los Alamos group was intimately involved in delineating the problems and in planning details of execution of the tests. However, many other groups played major roles.

There were thirty-three events characterized as "safety experiments"^(c) listed in the report on announced U.S. nuclear tests from the Nevada Operations Office and Los Alamos, Lawrence Livermore, and Sandia National Laboratories (NVO 1982). These were not all actual weapons. They were frequently associations of plutonium and high explosives in various configurations. Most of them produced zero fission release, but a few produced yields from a few tons of TNT up to the equivalent of fractions of a kiloton. Fortunately, all of the experiments that involved biology had essentially zero fission yields. All but one occurred at or near NTS, with one (Scaevola) taking place on a barge at Enewetak. The last experiment listed officially as a "safety experiment" occurred at NTS in October 1958. The shots for the Roller Coaster Project, which will occupy our attention soon, were listed as "storage-transport" related projects, rather than as safety shots because their primary objective was the development of criteria for transport and storage of nuclear weapons.

The bulk of the work concerned physical measurements, especially soil contamination and the physicochemical behavior of the released plutonium and associated actinides. This is true even of the long-term follow-up studies. Only two of the projects included extensive investigations of biological aspects, viz.,

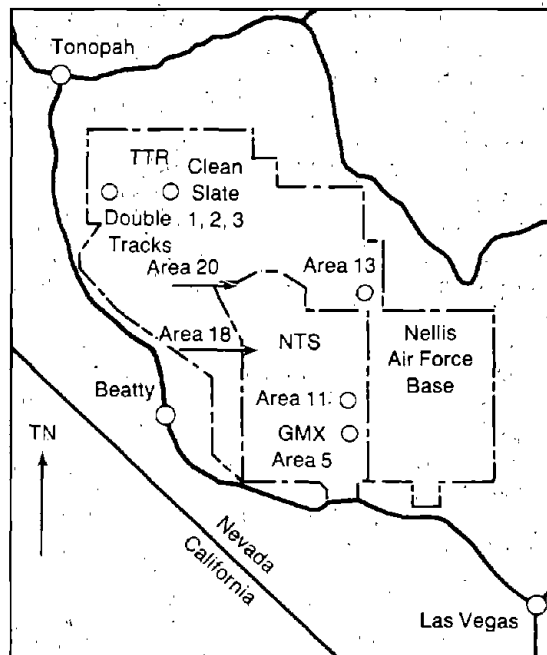
(a) Hence the term "one-point detonation."

(b) There was also a much-used classified document by Wright Langham, Payne Harris, and Ernest Anderson that we cannot quote.

(c) A safety experiment is defined in the quoted report as "an experiment designed to confirm a nuclear explosion will not occur in case of accidental detonation of the explosive associated with the device."

Test Group 57 of Operation Plumbbob and Operation Roller Coaster. Figure 14.1 shows the sites of most of the activities of interest. Details are given in the legend.

FIGURE 14.1. Map of Nevada Test Site (NTS), Tonopah Test Range (TTR), and the surrounding buffer region of the Nellis Air Force Range, in South Central Nevada. The areas involved are very large. The TTR was many miles from NTS. Project 56 activities took place in Area 11 (later referred to as "Plutonium Valley"). Test Group 57 was in Area 13, while Operation Roller Coaster took place at the points marked "Double Tracks" and "Clean Slate 1, 2, 3." The other areas designated were not involved very much in studies pertinent to this chapter. (Redrawn from Essington 1978.)



B. Project 56, GMX, etc.

Project 56 consisted of four shots done in Area 11 of NTS, two in December 1955 and two in January 1956. The purpose was primarily to test the vulnerability of current model weapons to one-point detonation. There was essentially no fission yield in two and on the order of one hundred pounds TNT equivalent in two tests (Johnson 1982).^(a) From the environmental standpoint, they were primarily useful in showing how the plutonium was spread, its behavior in air and soil, etc. There were fallout trays for collection and cement pads reinforced by air samplers, some of which were offsite. Otherwise there was nothing that could be tied into biological modeling and no overt biological work.

There were different configurations for the devices and thus different avenues of dispersal from total enclosure to essentially no obstruction. The objectives of the work were evidently met satisfactorily.

The reports of Project 56 remained classified for many years and were apparently gradually destroyed in the periodic housecleaning episodes that occur in government laboratories. Very little appeared in open publications. This author

(a) Johnson remarks that a "little fission helps because you are not put through the agony of 'hands and knees' alpha monitoring . . ."

is indebted to William Johnson, Sr. (cited above) and to Dr. Harry Jordan for a personal interview at Los Alamos (Jordan 1981) for reminiscences on the actual events. Fortunately, the long physical half-life of plutonium has made return visits to Area 11 possible and useful for checking out its persistence, any changes in mobility by processes of solubilization, its downward migration into the soil, the processes of resuspension by wind, and the ingrowth of ^{241}Am by the decay of ^{239}Pu .^(a) Later resurveys occurred under the aegis of the Nevada Applied Ecology group (NAEG) (which see).

The work of Project 56 and follow-up showed beyond question that plutonium becomes less available with time for resuspension by wind.^(b) This was pretty much a Los Alamos show. By a series of calculations based upon the findings of Project 56, lung models, and the like, the Los Alamos H-Division people came up with a figure for the maximum activity of plutonium that might be allowed without clean-up or evacuation around a Broken Arrow site. This was $100\text{ }\mu\text{g}$ of $^{239}\text{Pu}/\text{m}^2$ of surface. The figure has been largely attributed to Wright Langham and Payne Harris and seems to have been adopted, more or less verbatim, by the military (more of this in chapter 15). How it was derived appears to be lost in antiquity. The most quoted reference is a Los Alamos report by Harris, Anderson, and Langham (1956), but this author has not seen it for some years.

The so-called GMX shots were essentially chemical events, i.e., small chemical explosions that dispersed small quantities of plutonium. They were directed at "equation of state" physics studies. There were twenty-two GMX shots between December 1954 and February 1956. Their only biological contributions were through the soil-sampling program.

C. Test Group 57

There was considerable agitation for a much more extensive project than Project 56 to evaluate both the long-term and short-term hazards of the release of plutonium by a one-point detonation. In relatively short order, there evolved plans for a sophisticated study of the cloud dynamics and testing of fallout models, the behavior of the released plutonium in the air and in soil, ways to decontaminate various surfaces and vehicles, and a full-fledged biological experiment with both short- and long-term exposures. The Test Group was part of Operation Plumbbob, which took up most of the calendar year 1957. It began in early February 1957, with the shot occurring on April 24, 1957 at 0627, and the

(a) The work of Project 56 may have been classified, but the fact that someone was spreading plutonium around came to light through the Public Health Services' (PHS's) offsite surveillance work (see chapter 12). As Carter and Placák described (1956) at the AEC-DoD symposium on the shorter-term biological hazards of a fallout field, alpha contamination readings were obtained with fallout trays, with air samplers located in populated areas offsite, and a mobile air-sampler mounted on a trailer. Maximum contamination on a fallout tray was 10^5 d/min/ft^2 at a distance of about five miles from ground zero, but plutonium was detectable out to fifty miles. The portable air samplers showed plutonium out to one hundred miles. All of the readings were very transient and returned to background levels by the fourth or fifth day. They caused no concern regarding potential biological hazards offsite. Nevertheless, these facts indicate that quite significant quantities of plutonium must have been deposited onsite.

(b) This came from identical measurement techniques applied by the same people in repeat analyses at ninety days, one year, one and one-half years, etc.

field activities of the biomedical program were not completed until late October. The other field activities were completed much sooner.

The cloud dynamics and fallout model work included the use of balloons to suspend instruments above the array and was operated by the Sandia Corporation, which also did part of the longer-term air monitoring, surface monitoring, and the radiochemistry. The test director, James D. Shreve, came also from Sandia. The decontamination aspects were carried out by the U.S. Air Force. The biomedical program was assigned to the University of Rochester Atomic Energy Project with Robert H. Wilson as director of field operations, Robert G. Thomas as director of laboratory operations, and J. N. Stannard as general director for the biomedical program. The Armed Forces veterinary corps supplied two commissioned officers, Lt. Col. Roy Kyner, USAF, and Capt. Ralph Thomas, U.S. Army; an indispensable Sergeant First Class, Warren A. Gramley; and about twenty enlisted men to help handle animals. The thousands of plutonium analyses were done partly at Sandia in the laboratory of William Kingsley and partly by contractor organizations. Details of the planning, development of exposure cages and procedures, and of all operations are given in an unclassified report by Wilson, Thomas, and Stannard (1960).

The two distinct phases, acute and chronic, were handled somewhat separately. At the time of the detonation, twenty-four dogs were placed rather arbitrarily in a downwind array at five hundred, one thousand, and two thousand feet from ground zero. Also, about forty white rats were placed in cages on the ground for exposure to the passing cloud, and nine others were suspended in cages from the balloon rigging. Since the biological purpose of the acute phase was estimation of lung burden from inhalation of respirable particles from the passing cloud, recovery of most of the animals in the array occurred as soon as possible after it had been determined that there had been no beta-gamma radio-nuclides released in the shot. This retrieval was done, of course, in full protective clothing and respirators suitable for work in an alpha-contaminated field.

A few of the "acute dogs" remained in the field for several days after passage of the cloud. Some remained as long as thirty-six days (for details see Wilson, Thomas, and Stannard 1960). All rats were retrieved and sacrificed within four hours of the cloud passage.

It was not anticipated that the cloud passage would contribute much to the body burden because of the short period of exposure. In what turned out to be, in retrospect, a serious omission, no air samplers were placed at the animal stations for the acute phase.

Planning for the biomedical aspects of Test Group 57 concentrated mostly on the chronic exposure phase. It was reasoned that the windy desert environment would provide maximum opportunity for resuspension of the deposited plutonium and consequent inhalation by the animals. Thus, it was planned to place the animals for chronic exposure *after* the detonation to be sure to test only the uptake that might correspond to people living in a contaminated area, but not exposed to the cloud. The "magic" $100\text{-}\mu\text{g}/\text{m}^2$ line for plutonium on the surface was approximated by monitoring crews, and the animals were placed so as to be in the area from a maximum approximately ten times this nominal amount of surface contamination to a minimum of one-tenth of this figure.^(a) Thus, the

(a) The labor of defining the proper locations and placing the animals while the crews were fully suited-up in protective clothing and respirators was prodigious.

array was planned to put cages at grid points that would correspond roughly to 10, 100, and 1,000 $\mu\text{g}/\text{m}^2$ of plutonium surface contamination. There was, of course, horizontal spread along these lines to allow for shifts in wind direction. However, they were predominantly to the north and northeast of ground zero. Burros (nine) and sheep (ten) were added to the chronic exposure population to include animals that more closely approach the respiratory anatomy and physiology of humans than does the dog. A diagram of this grid pattern is shown in figure 14.2. The actual surface activities on the nominal 10-, 100-, and 1,000- $\mu\text{g}/\text{m}^2$ line were 2.6, 40, and 560 $\mu\text{g}/\text{m}^2$ as determined by the slow, laborious radiochemical analyses completed later.

The initial decisions had to be based on field-instrument measurements.

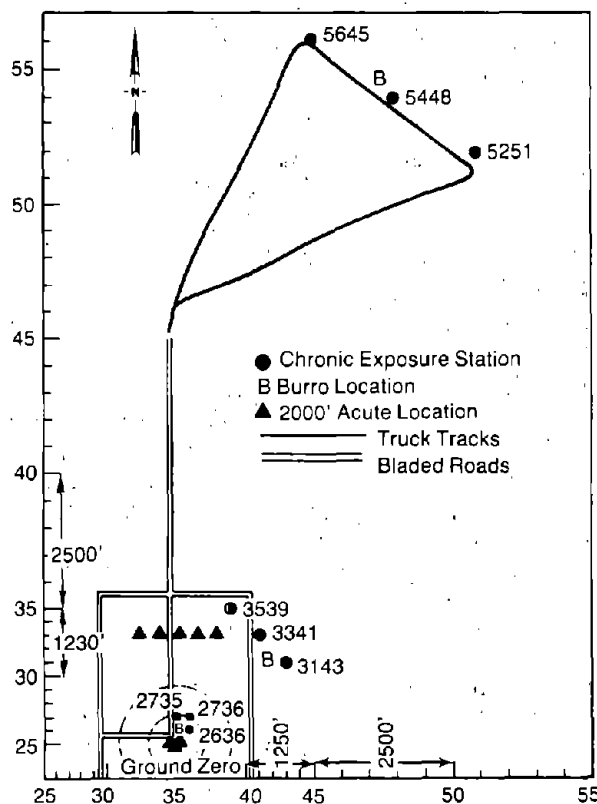


FIGURE 14.2. Layout of chronic array for Test Group 57 experiment. The 2,000-ft acute locations are also indicated for orientation purposes. The numbers refer to the grid coordinates for each cage complex. The first two digits refer to the north-south coordinate, the second two digits to the east-west coordinate. The nominal 1,000- $\mu\text{g}/\text{m}^2$ line was represented by 2735, 2736, and 2636; the 100- $\mu\text{g}/\text{m}^2$ line by 3539, 3341, 3143; and the 10- $\mu\text{g}/\text{m}^2$ line by 5645, 5448, and 5251. The array goes east of north because the prevailing winds are from the southwest. (Redrawn from Wilson, Thomas, and Stannard 1960.)

Animals were removed on a predetermined schedule ranging from 4 to 160 days after placement.^(a) The sheep and burros remained to the end of the exposure period. Some dogs were shipped back to Rochester at the close of the

(a) The logistics of maintaining animals in the field for so long a period needs comment. The Area 13 site was many miles from the supply base at Mercury and the usual route to it went directly across the areas where nuclear shots of Operation Plumbob were taking place. There were occasions when the dedicated animal-care crew drove several hundred miles to skirt the nuclear tests to get to Area 13 by a "back way."

160-day exposure period, and the plutonium burden in lung, rib, gastrointestinal tract, and both hilar and mediastinal lymph nodes in some was measured 360 days later or at 520 days after placement in the contaminated environment. Others were kept until it was clear that no long-term biological effects could be expected or detected, and they were then given to the Army.

Because the primary route of entry was expected to be inhalation, great emphasis was placed in the tissue analyses on lung, gastrointestinal tract, and the thoracic lymph nodes, but other tissues, particularly bone, were analyzed to measure redistribution from the lung.

The chronic phase had an elaborate program of air sampling. A cascade impactor operated by ground-laid cables from a central generator was planned for each fixed animal location. However, it was finally possible to operate only eight stations, one at each of the dog stations on the 10- and 100- $\mu\text{g}/\text{m}^2$ line and one at each end of the 1,000- $\mu\text{g}/\text{m}^2$ array. These were activated by Gast pumps. Rather than risk contamination in the field by removing and inserting slides and Millipore filters in the impactors in situ, the entire assembly was bagged and sent to Mercury for counting, and a fresh one was substituted. This occurred weekly. Technical problems prevented the air sampling program from getting into full operation until nearly a month after detonation, but it seems doubtful if this changed the basic results materially since the Sandia measurements were under way in the interim.

The results of this elaborate and laborious experiment can only be summarized here. There were some surprises, as will be evident below:

1. The animals exposed to the passing cloud showed much more plutonium in lung than expected. This was true also to a lesser extent for other tissues. Indeed, and despite the short period of exposure, the acute-phase animals showed generally higher body burdens of plutonium than even the longest-term chronic-exposure animals. In other words, it appeared that the short exposure to passage of the cloud was potentially more hazardous than chronic exposure to resuspended dust—totally unexpected.^(a)
2. The body and tissue burdens of the chronic exposure animals were much less dependent on the time of exposure than expected. Indeed, the readings were essentially random to the time of exposure. The expected gradual build-up in lung with time, for example, was not discernible.
3. As for correlation with location, the picture was mixed. Gastrointestinal tract and lung contents did seem to be fairly consistently higher at the nominal 1,000- $\mu\text{g}/\text{m}^2$ line than at 100 or 10 $\mu\text{g}/\text{m}^2$. This is illustrated in table 14.1A and B, which gives composite figures for all times. Note in table 14.1A that the relation to distance does not hold, however, for the lymph nodes. Neither did it appear to hold consistently for several other tissues listed in the table, but the amounts of plutonium were small.
4. The air concentration of plutonium fell off quite rapidly with time, $T_{1/2} = 35$ days. While the exact figure may be suspect because of the large variations, it is clear that the availability of plutonium for resuspension decreased rather rapidly. Thus, while total exposure increases with time, the increments

(a) This hazard may actually have been underestimated by the test, since, as Wilson (1984) commented, we have no assurance that the cloud-passage animals were at the location of maximum airborne concentration at ground level.

TABLE 14.1A. Test Group 57 "Safety Shot." Median Plutonium Concentration in Dog and Burro Tissues (disintegrations per minute per gram wet weight).

Exposure Condition	GI Tract Plus Contents	Hilar LN	Mediastinal LN	Lung	Femur	Rib
—Dog—						
Acute	25.05	2.05	3.45	0.71	0.046	0.56
1000 $\mu\text{gm}/\text{m}^2$	4.51	2.05	6.90	0.45	0.057	0.70
100 $\mu\text{gm}/\text{m}^2$	1.14	3.33	6.90	0.020	0.057	0.48
10 $\mu\text{gm}/\text{m}^2$	0.25	3.08	3.45	0.031	1.13	0.19
—Burro—						
1000 $\mu\text{gm}/\text{m}^2$		0.62		0.15		0.083
100 $\mu\text{gm}/\text{m}^2$		0.50		0.032		0.15
10 $\mu\text{gm}/\text{m}^2$		0.65		0.020		0.18

Source: Reset from Wilson, Thomas, and Stannard 1960.

TABLE 14.1B. Data on Lung and Gastrointestinal Tract Plus Contents (as a function of distance [acute], or isolevel line [chronic], expressed as median disintegrations per minute per organ. GI tract-to lung ratios).

Location	Lung	GI Tract Plus Contents	Ratio GI To Lung
—Acute Dogs—			
500 ft	47.5	2,742	58
1000 ft	95	72,109	760
2000 ft	101	15,699	157
—Chronic Dogs—			
1000 $\mu\text{gm}/\text{m}^2$	36	2,660	77
100 $\mu\text{gm}/\text{m}^2$	1.6	496	310
10 $\mu\text{gm}/\text{m}^2$	2.5	112	45
—Chronic Burros—			
1000 $\mu\text{gm}/\text{m}^2$	254		
100 $\mu\text{gm}/\text{m}^2$	41.8		
10 $\mu\text{gm}/\text{m}^2$	27.8		
—Chronic Sheep (P + 32)—(a)			
1000 $\mu\text{gm}/\text{m}^2$	34		
100 $\mu\text{gm}/\text{m}^2$	7.0		
10 $\mu\text{gm}/\text{m}^2$	0.4		
	(5.2)*		

* Numbers comprising the median lung values at 10 $\mu\text{gm}/\text{m}^2$ included one 0 dis/min. reading. However, the analytical data show that a spill occurred with the 0 value. Therefore, values including and excluding (in parenthesis) this value are shown.

(a) "P" = Placement day.

Source: Modified slightly from Wilson, Thomas, and Stannard 1960.

get smaller. It is not surprising that there was much less time-dependence than expected. This contrasts markedly with the usual laboratory experiment employing multiple exposures.

5. The air-sampling data showed that the amount of plutonium in air varied much less with distance than did the concentration at the soil surface. While ground concentration contours varied from 2.6 to 560 $\mu\text{g}/\text{m}^2$, a factor of about 200, the air concentrations varied by only a factor of about seven, even with the great variations in wind velocity characteristic of the Nevada desert. The air appears to be something of an integrator and shows as much where it has been as where it is when sampled, not surprising when one thinks about it. Wilson, Thomas, and Stannard (1960) point out that the ratios of high- and low-level lungs and gastrointestinal tracts are not greatly different from the ratio of the corresponding cumulative air samples.
6. When the long-term air-sampler data became available (it took considerable time to do the radiochemistry and obtain reasonably quantitative data), it appeared that the maximum potential airborne hazard at ground level occurred at a considerable distance from ground zero, in fact, more than twice as far out as the most distant animal arrays! (Remember a similar phenomenon occurred with fission products, as noted in chapter 12. It is probably related to particle size distributions in the cloud.)
7. Dosage calculations for lung, based on measured tissue contents, were considerably different from doses that could be calculated using acceptable models and the results of the air-sampling data. No easy explanation was forthcoming for these animal-instrument discrepancies.

Other reports on the more physical aspects of this extensive operation are contained in the closely related Weapons Test (WT) reports, some of them referenced by Wilson, Thomas, and Stannard (1960) and by Stannard (1973).

The work of Test Group 57 bolstered the working criteria for transport and storage of plutonium weapons. However, the unexpected importance of the acute phase, the lack of good physical characterization of what the animals "saw" in this phase, the small number of animals therein, and the partial collapse of the notion that the resuspended dust would be the primary culprit led to many questions and some dissatisfaction with letting things stand as they were at the end of the Test Group 57 effort. Hence, another still more extensive project was put into the planning stages—Operation Roller Coaster. We will consider it next.

D. Operation Roller Coaster

1. The Plan

Operation Roller Coaster provided the climax for active field projects built around possible one-point detonations. As we have seen, the work of Test Group 57, while extensive, left many questions unanswered, some of them newly raised by the results. Many doubted the validity of the criteria developed. The British, who had to rely on U.S. test data, were especially concerned. Their high population density and intensive land use had already led to adoption of more stringent allowable ground contamination levels and more stringent allowable exposures than those adopted by the United States (Wilson and Terry 1965a). A number of joint U.S.-U.K. conferences were held beginning in the fall of 1961. The lack of definition of the aerosols most involved in the cloud

passage and the new importance of the cloud passage phase led to design of a joint U.S.-U.K. operation to try to tie down some of the loose ends. This was approved in January 1963 with the United States being the principal agent for the field work, but the United Kingdom making important contributions of men and equipment.^(a)

Operation Roller Coaster was perceived as "a massive investigation of the nature and fate of the plutonium aerosol, physically, spatially and biologically" (Wilson and Terry 1965a, p. 275). The events took place in an area of the Nevada desert even more isolated than NTS—an area northwest of NTS toward Tonopah (see figure 14.1) known as the Tonopah Test Range (TTR). There were participants from many quarters, military and civilian, as can be seen from the listing of reports to be presented later. Robert H. Wilson was the project officer with special responsibilities for the biomedical aspects, but the University of Rochester did not carry the major burden for these aspects as it had for Test Group 57.^(b) Indeed, the operation involved so many different organizations and people that the relative speed and high quality of the results must be marveled at. Obviously, coordination was very effective, as is possible in a military-type operation.^(c)

It was originally planned to repeat the work of Test Group 57 but on a much larger scale, both physically and biologically. However, it was not feasible to mount animal studies for the resuspension phase on so large a scale. The potentially greater hazard of the cloud passage phase led to a decision to concentrate the animal exposures on this. Resuspension phenomena, which were studied over a 160-day period, were studied by air-sampling instruments alone.

There were four detonations in the Roller Coaster operation under code names, "Double Tracks" and "Clean Slates I, II, and III." Double Tracks was arranged to minimize the entrainment of nondevice constituents into the cloud by firing on a large steel plate placed on a larger concrete pad both in a 100-ft circle of stabilized desert soil. There was a 78-mi² instrument array extending more than nine miles downwind. Clean Slate I simulated an open storage or transport accident, while Clean Slates II and III were fired in typical high-explosive magazines. The assumption had been made in the United States that a cover of earth would reduce the concentration and modify the aerosol of plutonium. Each of these Clean Slate shots had extensive instrumentation like Double Tracks. However, the major biological involvement took place in Double Tracks plus limited participation in Clean Slate II.

The animal studies of Operation Roller Coaster were the "largest inhalation investigation ever performed under field conditions," (Wilson and Terry 1968, p. 23) with 98 dogs, 154 sheep, and 98 burros, including controls (22 sheep, 14 dogs, and 14 burros). The increase in large animals over Test Group 57 was to provide more data from animals with greater potential applicability to humans than the dog has.

Reports of Operation Roller Coaster are relatively numerous, but only a few are generally available. There were many interim and progress reports, since all

(a) The British have long been strong in the areas of air sampling, aerosols, and meteorology and supplied particular help in these areas and much in the general planning.

(b) T. T. Mercer provided assistance with the aerosol evaluation, P. E. Morrow with interpretation of the biological results, and A. M. Dutton provided statistical analyses. All of these were from the University of Rochester.

(c) Regarding U.K. participation, Wilson and Terry (1968) mention especially A. Robson, R. Carter, and D. M. C. Thomas in addition to their coauthor, K. Stewart.

concerned were anxious to use the results as soon as possible. For our purposes, four documents, two of them already cited, provide the most pertinent biomedical information: the University of Rochester Atomic Energy Project Report by Wilson and Terry (1965b); the published paper at the symposium on inhaled particles and vapours, also by Wilson and Terry (1965a); a POR-WT report from the Defense Atomic Support Agency by Wilson and Terry (1968); and a final evaluation from the U.K. Atomic Energy Research Establishment (Stewart and Wilson 1968). Other more or less complete reports in the POR-WT series (i.e., joint U.K.-U.S. efforts that had "POR" designation, that stood, I believe, for "Project Officer's Report") were not specifically oriented to biology. They are listed as note 1 at the end of this chapter. The installations and personnel involved are listed there along with the other information.

The four main biomedical reports were not mutually exclusive. However, each has information not found in the others. Even though most of the documentation is in report literature and little in open publications, it cannot be said that this operation suffered, as did Project 56 and to a lesser extent Test Group 57, from inadequate reporting of some aspects. Nevertheless, the reports form a somewhat disparate mass that has not been graced by a concise overall summary. In the section to follow, we will consider very briefly the biological operation and the conclusions therefrom.

2. The Biological Experiment and Aerosol Support

Since the emphasis was to be placed on exposure during cloud passage, an entirely different mode of exposure for the animals was devised compared to Test Group 57. Instead of fixed placements, the animals were positioned on farm wagons (thirty of them) with either cages for the dogs and sheep or stanchions for the burros. These wagons could be moved along the designated arcs in the event of small changes in wind direction, which helped to remove some of the constraints on meteorology at the time of the shot. Also, to minimize ingestion by licking of fur, animal clothing was designed of muslin sheeting held in place with upholstery tape. These shrouds were found by preliminary tests to greatly reduce the noninhalation components of the exposure. They also simplified greatly the process of decontamination after the shot.

All of this was good for the experiment. Nevertheless, it generated a preshot procedure of considerable magnitude, viz., shroud over three hundred animals, load them onto thirty farm wagons, draw the wagons several miles from the base of operations to the shot site, place the wagons on the various arcs, and be prepared to change location up to minutes before shot time. Obviously, a fairly long and intensive training period was required for all hands, human and animal, to make such a program work.

Each wagon carried a Casella Mark II cascade impactor and a battery-driven Austin pump. In addition, some wagons had total air samplers (Mark I), Gelman disposable samplers, and Casella impactors with nuclear track stripping film. Every effort was made to have the samplers as close as feasible to the animals' noses.

Full details of these preparations and the shot-time, as well as those after the shot operations are given by Wilson and Terry in the University of Rochester report (1965b).

Although the intent was measurement of pick-up by the animals from cloud passage, the measurement schedule for the animals was quite long. It was intensive in the first month, but some animals were not sampled until three years

after the shot to check on retention factors. Over two thousand plutonium analyses were generated by this segment of the operation alone. The results, naturally, did not appear overnight.

3. The Results

Despite every attempt at its avoidance, random variability was as inherent in this experiment as the earlier ones. However, the sheer mass of data made the discernment of trends less irksome.

The results that came largely from the reports of Wilson and Terry (1965a,b) are summarized below:

- a. The aerosols were well characterized thanks especially to the expert contributions of the U.K. participants. Fairly large particles frequently contributed sizeable fractions of the total activity. Nevertheless, the early analyses of lung burdens showed close relationships to the information from the air samplers. "An animal is a competent sampler" (Wilson and Terry 1965a, p. 281).
- b. Initial deposition was about 23% of the respirable aerosol in dogs, about 11% in sheep, and about 18% in burros.
- c. Short-term clearance half-times were about four days for dogs, five days for sheep, and about ten days for burros.
- d. The sheep cleared much more plutonium by fast component kinetics. Thus, the amount of plutonium left for long-term clearance differed considerably among the species: 67% of the initial burden in dogs, 5.1% in sheep, and 22% in burros.
- e. The clearance kinetics for the Clean Slate II shot, which had much more inert dust, were different. Much more was cleared by dogs and sheep in the first seven days (Wilson and Terry 1965a, p. 285). As a result, the remaining lung burdens at seven days were only 5.5% of the respirable aerosol for Clean Slate II versus 15.9% for Double Tracks in the dogs and 0.4 versus 2.1 in the sheep. The organizers of the project had occasion to wish that they had been able to devote as much attention to these differences and aerosol-animal interactions as they did to Double Tracks, since they could influence hazard evaluations.^(a)
- f. The findings indicated that neither animals alone nor samplers alone would have sufficed to describe the respiratory hazard. Yet, the relatively good agreement between the two contrasts with the earlier tests and with much industrial hygiene experience.
- g. Mean radiation doses to infinite time for the three species studied ranged, for the aerosol of Double Tracks, from 0.96 rem in the dog to 0.08 rem in the sheep. The extrapolation to humans was 0.3 rem.
- h. There was little evidence of build-up of plutonium in tissues other than lung, and possibly respiratory lymph nodes. Thus, for this exposure, the lung appears to be the critical organ.

In the final evaluation (Stewart and Wilson 1968), the same basic points were confirmed, but there was much more: (1) on the kinetics of lung clearance, including the fact that a power function fits the data; (2) on the reliability of the characterizations; (3) on the point that the patterns of PuO₂ behavior in the

(a) This may be a non sequitur since the tendency is always to choose the most conservative case, and that would be the cleaner aerosol for Double Tracks, which was studied most extensively.

dog seen in this field experiment are very similar to those found in laboratory experiments; and (4) showing that the results from each animal species form a consistent set, i.e., the differences are not random. There was a tendency to view the burro as the best model for humans.

The difference between Double Tracks and Clean Slate II aerosols led to calculation of a factor of about three difference in the ten-year dose to lungs, with the Double-Tracks-type aerosol the higher.

In all the reams of data and discussion, it is hard to find a simple succinct statement from the investigators that Operation Roller Coaster did or did not confirm the importance of the cloud passage uptake and doses versus those from inhalation of resuspended material as drawn from the work of Test Group 57. However, since the cloud passage data are used for the calculation of dose, the discussion of hazard, and development of criteria, we must assume that the answer to this question was affirmative, although the planning was such that little else could be expected.

4. Comment

Plutonium radiochemistry is a slow process. It appears that one reason there seems to have been no grand finale in the reporting and analysis of either Test Group 57 or, especially, Operation Roller Coaster, is that there are still data requiring analysis. A letter from R. G. Thomas to R. H. Wilson (Thomas 1981) raises the question of what may or may not be waiting and also refers to the many soil samples taken by the University of California, Los Angeles (UCLA) team (especially Kermit Larson) in Area 13 that remain unanalyzed. We will see in a later section that conscious attempts have been made to go back over these contaminated areas (see the section on the NAEG). Yet, there seems to be some possible unfinished business from these two major operations.

E. Palomares and Thule

The Palomares and Thule incidents were accidents, not planned projects, and thus were not "Safety Tests." Yet, they need to be mentioned in this review. The one at Palomares, Spain, occurred on January 17, 1966. As a result of a refueling accident (collision) involving a B-52 bomber and a KC-135 tanker over the Mediterranean Ocean, four nuclear weapons were released from the bomber. Two were recovered intact, one from the Mediterranean about five miles offshore and one from a dry riverbed east of the Spanish village of Palomares (population about 1,000), on the coast. The other two underwent high explosive detonation, one at the east edge of the village, the other about one mile to the west. With a thirty-knot wind blowing out of the west, the dust containing ^{239}Pu , ^{234}U , and ^{235}U travelled across irrigated fields at the edge of the village in the one case and over truck garden areas just outside of town in the other. There was no nuclear yield in either.

The Thule incident occurred on the ice near Thule, Greenland, when an on-board fire forced ditching of a B-52 aircraft on January 21, 1968. Again there were detonations of the high explosive charges and contamination of the environment with plutonium, but no nuclear yield.

As mentioned earlier, these internationally important events were described briefly in an open literature publication by Stannard (1973). Much more detail is hidden away in the general discussions of plutonium contamination of the environment by Langham (1968, 1969, and 1971), in a trip report concerning his

return visit to Palomares and the collaborative efforts with the Danish at Thule (Langham 1972); and, for Thule, a special edition of the journal *USAF Nuclear Safety* entitled, "Project Crested Ice" (USAF 1970).^(a) The primary actions were to remove as much of the plutonium as possible from the surface and ship it back to the United States. Residual contamination at Thule was minimal since the plutonium that was not removed was gradually diluted into the sea. However, there were full-fledged examinations of biota and an extensive ecological program managed primarily by the Danes (Aarkrog 1971a,b; 1977), and by W. C. Hanson of the Hanford Labs (1971, 1972, 1975).

Langham (1972) describes the continuing work at Palomares carried out largely by a joint effort of the Junta de Energia Nuclear Division de Medicina y Proteccion headed by Dr. Eduardo Ramos, with equipment and operational support from the AEC. After the clean-up of the most contaminated area,^(b) the project settled down to periodic surveys of the environment and occasionally of the inhabitants. Long-term contamination levels of humans or environment have not been sufficient to cause real concern. The levels of airborne plutonium and uranium within the village were consistently below the maximum permissible concentration (MPC) (Iranzo and Salvador 1970). Samples nearer the sites of impact recorded maximum values of gross alpha activities above the MPC on fourteen occasions in the second half of 1966 and in 1967. The MPC was exceeded by a factor of ten on three days. These were during periods of high winds and much resuspension of the deposited radionuclides. Interestingly, the incidence of measurable uranium in the air exceeded that of plutonium; 30% of the samples showed no trace of plutonium, while only 3% showed no trace of uranium.

This work is continuing, albeit at a relatively low level.^(c) Fortunately, both of these incidents occurred in areas of low habitation density. Unfortunately, for the measurements, the area around Palomares happens to have one of the highest alpha-particle backgrounds in Spain, and the low-level measurements easily got lost in it.

Finding more detailed technical evaluations and their contributions to internal emitter research and hazardous analysis is not easy. The joint Spanish-U.S. reports and Spanish in-house reports would be useful, but are not readily available. The most convenient summary for the technical reader of the work done at Palomares over the first several months is a paper by Odland et al. (1968)^(d) given at the seventh Hanford biology symposium (see chapter 8 for these symposia) and the International Radiation Protection Association (IRPA) report by Iranzo and Salvador (1970), which concerns longer periods. The results reported

- (a) The author has copies of these documents that he would be glad to make available to interested readers. They are unclassified. There are also book-length descriptions of the events themselves and much in news magazines of the day (see Odland et al. 1968).
- (b) The ugly scar left on the fragile semiarid landscape, from the clean-up operation, impressed Langham as the most significant long-term result of the incident.
- (c) It was the author's privilege to meet Dr. Emelio Iranzo, Dr. Ramos's colleague in the Spanish operations, at the 1984 meeting of the Health Physics Society and to be informed that the work is still under way.
- (d) This paper gives rather complete references to descriptions in the popular press (*Business Week*, *Commonwealth*, *Life*, *Newsweek*, *Saturday Evening Post*, *Saturday Review*, and *U.S. News and World Report*) and reports from the PHS. A book-length description by Lewis (1967) is also cited.

by Odland include analysis of urine samples, nose swipes, water from various sources, such as the Mediterranean Sea and shower effluents, and radioactivity in soil and on vegetation samples. The urine samples came primarily from Air Force, Army, or Navy personnel involved in the clean-up operations. Only 38 out of 1,586 were other, and it is not clear whether or not these were residents. (Probably the prime source of data for the residents is in the Spanish literature, and this contained mostly long-term concentrations in air.) The plutonium analyses were done, for both initial and resamples taken several months later, by the U.S. Air Force Radiological Health Laboratory. Systemic body burdens of plutonium were calculated by the Langham equation for a single acute exposure (Langham 1956; for further discussion see chapters 7 and 16).

Of the 1,586 urine samples analyzed for the acute phase operations, 20 showed calculated body burdens greater than the maximum permissible, 422 showed plutonium concentrations between 0.99 and 0.09 of this value, 537 showed values between 0.09 and 0.009 of the above, and 607 showed calculated body burdens less than 0.009 of the maximum permissible. When we consider that these came from a hastily gathered group of personnel brought in for the acute phase of the operation, such a distribution of body burdens may be considered as satisfactorily low. However, these individuals wore protective clothing and took precautions that an uninitiated, untrained resident might not.

The nose swipes in the Odland work were negative, and the amounts in vegetation (e.g., tomatoes) were lower than reported in some of the magazine versions. However, the crops were condemned anyway.

The Air Force operated a resampling program for urinary plutonium content involving 422 personnel; all but 7 of them military. There were 6 cases with greater than 10% of the allowable systemic body burden, 213 were between 1% and 10%, 39 less than 1%, and 164 below the limits of detection.

One individual died during the study, of causes unrelated to plutonium exposure. The plutonium content of lung was about 500 pCi, calculated for the whole lung, while the last urine sample showed no detectable activity. This suggests the possibility of insoluble deposits of plutonium in lung and the virtues of resurveying the group with whole-body counters.

In view of the probable lack of protective actions taken by the Spanish residents and the airborne concentrations of alpha activity reported (e.g., by Irazzo and Salvador), it is surprising that there have not been reports of significant body burdens in any of these individuals. It can only be speculated whether this means that the levels were consistently low, the necessary measurements difficult, or not done, or the reports not generally disseminated. It is also surprising that measurements appear not to have been made in the indigenous animals and that animals were not brought in as stand-ins for humans (Wilson 1984).

The plutonium at Palomares does not seem to have descended very far into the soil; perhaps to be expected in a semiarid climate. Population and commercial pressures are prompting the inhabitants to expand gardening activities ever closer to the contaminated area (W. J. Bair, personal communication, October 1985). This makes it essential that the monitoring and survey activities be continued. It even augers for possible pressure for more removal of surface and near-surface soil for disposal.

Further follow-up of Palomares is reputed to be under way by personnel from several American laboratories under the Department of Energy (DOE): Los Alamos National Laboratory (LANL), Lawrence Livermore National Laboratory (LLNL), Oak Ridge National Laboratory (ORNL), as well as DOE Headquarters.

and by the Spanish authorities (e.g., Iranzo). No information has appeared that would change the conclusions drawn above.

Similar summaries of personnel monitoring for the Thule event, from both Danish and U.S. sources, are contained in *USAF Nuclear Safety* cited above. However, few quantitative data are given there. The emphasis is more on the environment. This is as it should be by the circumstances of the event, and much important information is contained in this review. A succinct summary and analysis of the work of Project 56, Test Group 57, and Operation Roller Coaster and how this work made it easier to react effectively to the accidents at Palomares and Thule were written by Harry Jordan at Los Alamos. His summary refers to some of the classified reports from the Nevada operations and gives also details on the contents of the Air Force document, "Project Crested Ice," cited above (Jordan 1971).

A resurvey of eight locations near Thule was carried out in 1974 (Hanson 1980) as part of a general review of the concentrations and inventories of ^{137}Cs , ^{238}Pu , and $^{239, 240}\text{Pu}$ in soils, lichens, and animals from northern Alaska and Greenland. Average inventories of $^{239, 240}\text{Pu}$ of Thule lichen communities, not directly contaminated by accident debris, were not significantly different from those in Alaska lichen carpets in 1968 and 1974, respectively. Thus, the Thule area was no higher six years after the incident than other Arctic areas possessing the unique lichen step in the food chain. Soil samples contained about 10^{-15} Ci of $^{239, 240}\text{Pu}/\text{g}$.

More details of the Thule ecological work can be found in publications by Aarkrog (1971a,b; 1977) and by Hanson (1971, 1972, 1975). These papers concern primarily the transport of plutonium in the subject ecosystems and are more appropriately considered as part of chapter 15. Much hinges on the $^{239, 240}\text{Pu}/^{137}\text{Cs}$ ratios.

III. Long-Term Follow-Up— The Nevada Applied Ecology Group

A. Genesis

In 1970, the AEC established an organization known as the Nevada Applied Ecology Group (NAEG) whose purpose included the following objectives:

1. Determine how and to what extent radioecological processes had redistributed plutonium and determine its uptake and food-web pathways in the biota of the NTS.
2. Guide and coordinate ecological, radiation monitoring and other environmental programs necessary to support continued nuclear testing activities.
3. Provide the mechanism to effectively comply with the requirements of the National Environmental Policy Act (NEPA) of 1969.

The program was planned and administered by a small scientific staff based at Nevada Operations Office (NVO). Principals in developing and administering NAEG were Jared Davis and Ernest Campbell, with the enthusiastic support of the NVO General Manager, R. E. Miller. Later the program was administered by Paul Dunaway and M. G. White, under the NVO General Manager, General M. E. Gates. Funds for the program were distributed to many laboratories through the NAEG operations. Prime among these were: the AEC family, the Pacific Northwest Laboratory (PNL), Battelle Columbus Laboratory, LANL, LLL, UCLA, ORNL, the AEC's Health and Safety Laboratory (HASL), New York, and

National Reactor Testing Station, now the Idaho National Engineering Laboratory (INEL); and outside of AEC, the Environmental Protection Agency (EPA) and Air Resources Laboratory, National Oceanic and Atmospheric Administration (NOAA), Las Vegas and NTS, Nevada; the University of Nevada at Las Vegas and service contractors such as REECO and Rockwell, Hanford. Many others joined for specific tasks.

B. The Problems and Mode of Operation

The scientific problems attacked were varied. High priority was given to soil analyses. There was much interest in what had happened to the plutonium in the years since the shots and whether or not the solubilization processes demonstrated in earlier laboratory and field research lived up to expectations in a larger-scale, larger-area study. There was also interest in the nature of the soil-plutonium binding processes, both physical and chemical; the increasing role of americium, the processes of resuspension by wind (which we will discuss in chapter 15), and how all of these could be brought to bear on hazard analysis. An enormous effort was put into statistical analyses to guide the soil sampling procedures for example and for interpretation of the data.^(a)

There was also much work with grazing animals and native animals, including uptake and transfer from vegetation, the construction of models for the possible intakes by and doses to humans developed from the accumulated data, and some very cogent laboratory investigations of specific points raised by the findings in the field. Finally, as momentum accumulated for the development of a full-scale information repository at Las Vegas, the NAEG entered into the work of the Information Center (see chapter 12). One of the earlier steps was a selected annotated bibliography on the environmental aspects of plutonium prepared by the Division of Technical Information, USAEC and spearheaded by Helen Pfuderer with guidance from M. G. White and others (e.g., ORNL 1972 with many updates; and 1978).

The various individuals and laboratories engaged in work for the NAEG program labored at their home institutions. Communications were handled by periodic NVO reports and an annual symposium, usually held in Las Vegas, that brought the principal investigators together for in-depth progress reports and discussion of plans. There was also an advisory committee for the general operation and several advisory committees for specific areas of research. We will discuss a few areas of special pertinence to this chapter presently. A selected list of reports is given as note 2 at the end of this chapter.

Before proceeding, however, we should remark that one of the prime early objectives of the NAEG, *not spelled out in the official raison d'être*, was to establish an inventory of the transuranics present at NTS and adjacent sites. Was there a sufficient amount of plutonium and the transplutonics to warrant clean-up measures? While Areas 11, 13, GMX, Tonopah Test Range^(b) are now among the more unlikely places for human habitation, it was argued that some day cheap irrigation water (desalinated sea water?) and the pressures of world population might change all that. People might live and grow crops in the midst of these long-lived radioactive materials! Thus, the inventory in the soil, its

(a) Until one reads these extensive compendia, it might have been thought that digging a suitable soil sample would be a simplistic if back-breaking process. Not so! It is a highly technical affair.

(b) Tonopah itself has a population of a few thousand and is growing.

availability, and the amounts found in grazing and indigenous animals and in vegetation assumed more than academic significance. We will review some of the key findings in the light of this erstwhile improbable environmental question.

C. Soil Sampling

The soil sampling program of NAEG was designed initially by the people at Los Alamos. Eric B. Fowler, whom we have already met, became chairman of the Soil Sampling and Analysis Committee, which was responsible for the plans and conduct of a radionuclide inventory study at five sites: Project 57 in Area 13; GMX in Area 5; Sites A, B, C, and D in Area 11; Clean Slates I, II, and III at TTR; and Double Tracks at a site adjacent to the Tonopah Range (see figure 14.1). From the beginning, R. O. Gilbert from PNL collaborated in the statistical design of the work and analysis of the data. Essington (1978) gives a good summary of the historical development of the soil sampling programs.

"Safety shot" sites were sampled intensively for ^{238}Pu , $^{239,240}\text{Pu}$, ^{234}U , ^{235}U , ^{236}U , ^{238}U , and later ^{241}Am . Detailed soil sampling was done by laborious and carefully designed procedures, followed by wet chemistry analyses. This takes much time. There was, in addition, in situ measurement of soil activity with a moderately portable instrument (Field Instrument for Detection of Low Energy Radiation [FIDLER]), also by Geiger-Müller and alpha survey measurements. However, the area was too large to be covered in detail on foot. Therefore, airborne gamma-radiation surveys were included. Under proper circumstances these could pick up the 60-keV gamma radiation from ^{241}Am and thus any "hot spots" missed in the other work could be detected and ground crews dispatched to check on details.

Among the earlier reports was a series of papers from NAEG-supported laboratories at a symposium sponsored by the International Atomic Energy Agency (IAEA) on transuranium nuclides in the environment held in San Francisco in November 1975. Despite the interest in the total inventory, these papers give it scant overt attention. Much more is said about movement in soil with time, chemical form, particle size, contours of distribution, etc. Only one paper addressed the central problem openly. Gilbert et al. (1976) reported on the inventory of several nuclides and gave an estimated inventory of $^{239,240}\text{Pu}$ in surface soil at one site (designated "A") in Area 11. It totaled about 0.035 Ci in three strata. There was much more uranium, but much of it came from natural sources. Other data, including inventory of other sites, were shown at later annual NAEG meetings and in publications. However, any composite figures for the total inventory appeared to be almost impossible to assemble. If they were, they would probably be classified. Nevertheless, we can find the trend of thinking several years after NAEG began operations in a partly philosophical, partly technical paper from the UCLA group (Wallace and Romney 1978). Their answer to the clean-up question is shown as part of their recommendations, quoted below:

Relatively little hazard exists with the Pu present at the old safety-shot sites in Nevada because so little human activity occurs or is likely to occur there, because the grazing potential of the amount of land in question is so negligible, and because no irrigation schemes for the area are likely for decades or centuries. It seems, therefore, that it would be valuable and profitable in behalf of mankind to obtain more of the answers possible from the presence of Pu in the natural desert environment. (Wallace and Romney 1978, p. 124)

Thus, the decision regarding clean-up was resolved in favor of no action for the present. The need for gathering more information took precedence. The quoted paper and its bibliography present some of the ideas about possible clean-up methods and their relative impacts should the decision be made to undertake it. Other aspects of the work with soils can be illustrated by the following:

1. Essington et al. (1976) showed from examination of over seventy individual soil profiles that there can be both smooth leaching of the transuranics and accumulation within specific zones; also, that large amounts can be found in the deepest profile.
2. Plutonium at NTS is predominately (50% to 70%) associated with coarse silt, 20 to 53 μm (Tamura 1976).
3. Much information was gathered that showed that microorganisms can contribute significantly to bioavailability and transport of plutonium in the environment. For example, plutonium went into the spores of the bread mold (*Aspergillus niger*) and could be transported to other soil fractions or the biomass by this route.^(a) This phenomenon was described at the IAEA symposium by Beckert and Au (1976) and in more detail at the 1978 NAEG meeting (Au and Beckert 1978). The work by NAEG confirms and extends the similar findings reported in chapter 13.

The Battelle people were also finding effects of microbiological processes on the behavior of transuranic elements in soils, plants, and animals, as was mentioned briefly in chapter 13. A useful review is contained in the book by Hanson, *Transuranics in the Environment* (Wildung and Garland 1980).^(b)

4. Much more was done with soils, including ideas on how rapidly the downward migration occurred, the bearing of the findings on protection criteria and sampling of many of the nuclear detonation sites, all of which we will have to pass over here, except to recommend that the reader peruse the list of NAEG reports in note 2 and the references in those papers.

D. Plant-Soil Interactions

Work on plant-soil interactions was largely done in the laboratory and followed closely that reported in chapter 13 even to having it concentrated at UCLA (Romney, Wallace, and Kinnear 1978). Support for the work came from NAEG because of the importance of knowing more about root uptake to answer the question of the need for cleanup. The results confirmed those discussed in chapter 13.

E. Vegetation

An overview of the findings with vegetation can be gleaned from the abstract of a paper by Romney et al. (1976) given at the IAEA symposium.

- (a) *Aspergillus* was especially useful since the spores are well above the growing mass of mycelia and can be harvested with little danger of contamination from soil or other organisms. There is reason to suppose that many soil microorganisms contribute to such processes.
- (b) Much of this was laboratory work or was done onsite at Richland and, thus, is not entirely associated with the NAEG effort.

Vegetation Studies in aged plutonium fall-out areas showed variations in the $^{239,240}\text{Pu}$ and ^{241}Am contamination levels attributable to differences in the amounts of resuspendable particulate material superficially entrapped upon plant foliage. There was reasonable agreement between the mean activity levels in vegetation and soil samples collected across different activity strata defined by FIDLER survey instrument within each fall-out area. The ratio of vegetation Pu to soil Pu tended to increase, moving out from higher to lower activity strata, which might reflect the increasing proportion of finer particulate material initially deposited in fall-out debris at greater distance from ground zero. The Pu/Am ratio was reasonably constant for vegetation samples collected from a given fall-out area. This ratio, however, varied among separate test events, primarily as the result of differences in the ingrowth of ^{241}Am within the aged source materials. Inventory estimates indicate that standing vegetation contributes a rather insignificant portion of the total contaminant remaining in these aged fall-out areas. (Romney et al. 1976)

Details were added in further work but nothing fundamentally different.

F. Grazing Studies

Probably some of the most pertinent information for biomedical evaluations came from the grazing studies carried out by the EPA Environmental Monitoring and Support Laboratory in Las Vegas and its branch at NTS,^(a) as described in chapter 13 and by Smith, Barth, and Patzer (1976) and Smith (1978, 1979). The first work involved only seven cows, four calves, three fetuses, three goats, three foxes, one jack rabbit, and one coyote; however, the later studies were much more extensive. They even involved the fistulated steers described in chapter 13. The studies presented a wealth of information. Since the cattle were restricted to the contaminated area, whereas the wild game had a much wider range, the cattle had higher contents of actinide nuclides than did the wild game.

Smith (1979) gives the following broad survey of ^{239}Pu activities in tissues of grazing cattle:

- from minimum detectable to 5 pCi/kg—kidneys, muscle, blood, whole fetus;
- from 1 to 20 pCi/kg—bone, liver, and gonads;
- from 10 to 100 pCi/kg—lungs;
- from 100 to 500 pCi/kg—tracheobronchial lymph nodes.

In a 1978 paper, Smith gives figures of <1,000 pCi/kg for rumen fluid, <5,000 pCi/kg for rumen vegetation, and <20,000 pCi/kg for skin and hair. Thus, the poor absorption of plutonium seen in laboratory experiments does not seem to have been changed much by the effects of environmental "weathering."^(b)

The finding of essentially equal amounts in bone, liver, and gonad was unexpected since laboratory work, quoted in earlier chapters, showed much less plutonium in gonad than in bone or liver. Smith points out the need for further follow-up. However, the NAEG is suffering from funding cuts and diversion of activity to the more general follow-up of fallout phenomena. This author has not found further confirmation of this finding.

(a) Formerly part of the Southwestern Radiological Health Laboratory.

(b) Note, however, that this work covers only a few years of such weathering.

Note that the units used above are picocuries per *kilogram* of tissue rather than per gram. Thus, the absolute amounts are not of immediate concern. Yet it must be remembered that these figures were from only a few years of grazing, and long-term accumulation or lack of it over many years of grazing in a contaminated area has not yet been ascertained.

Other work with large animals covered mechanistic items such as the metabolism of americium in dairy animals, solubility of actinides in ruminal gastrointestinal contents, and the resulting predicted tissue retention and milk secretion of field-ingested ^{241}Am , and other work linked to the laboratory studies described in chapter 13, except that they were done under the aegis of the NAEG.

G. Modeling

To further the goals of the NAEG, preliminary models were constructed of potential plutonium transport pathways from the environment to humans, partly to be sure the field work did not miss some important step. This work was spearheaded by W. E. Martin and S. G. Bloom at Battelle Columbus Laboratories (BCL). A version based on moderately early information from the NAEG studies was constructed to provide a basis for stating the probable rates of ingestion and inhalation of plutonium by a hypothetical Standard Man living in a plutonium-contaminated area like those at NTS. The parameters for metabolism once in the body were based on publications and recommendations of the International Commission on Radiological Protection (ICRP). This model was presented at the IAEA symposium on transuranic elements in the environment (Martin and Bloom 1976). Estimated doses due to inhalation and ingestion of ^{239}Pu , over a fifty-year period, were given as factors by which to multiply the average concentration of ^{239}Pu in the surface soil of the reference area. With this parameter expressed as picocuries per gram, the factors to translate to rem in fifty years turned out to be: 0.6 for thoracic lymph nodes, 0.025 for lung, 0.015 for bone, 0.01 for liver, 0.003 for kidney, 0.0007 for total body, 0.0003 for gastrointestinal tract.^(a) Note there is no figure for gonad and that the figure for gastrointestinal tract must involve much self-absorption. The authors show predicted dose commitments from ^{239}Pu and cumulative doses for fifty years in Standard Man living in an average NTS area. Lungs, bone, and liver approach 5×10^{-2} rem, thoracic lymph nodes approach 10^0 rem.^(b) They also calculate an MPC in soil on the order of 3 nCi ^{239}Pu /g soil, or about $270 \mu\text{Ci}/\text{m}^2$. Presumably, this equates to a lung dose rate of 1.5 rem/yr.

There were modifications in the model as work progressed (Martin and Bloom 1977) and an analysis of the effects of variations in source term and parameter values on the estimates of radiation dose to humans (Bloom and Martin 1978). As expected, fairly reasonable variations in such things as particle size and translocation class for inhaled material can make very large differences (several hundredfold) in the calculated dose. Thus, any single figure from models such as these cannot be used except for range-finding purposes. Naturally, quite conservative assumptions are usually made, so any final numbers quoted will usually be ultraconservative. We will return to some of these matters in connection with the work on setting soil standards to be discussed in chapter 15.

(a) Inhalation accounts for all of the dose predicted to thoracic lymph nodes and lungs, and for about 94% of the predicted dose to bone, liver, kidneys, and total body.

(b) Read from figure 5 of Martin and Bloom (1976).

H. Comment

The description above considers only a part of the work of the NAEG since it relates only to the actinides. Much was done also with fission products. A broader review can be seen from the report listing and contents in note 2.

As indicated earlier, the question was asked as to whether or not the work of NAEG on the safety-shot sites had not reached a logical termination point. Wallace and Romney (1978) could muster numerous cogent reasons for continuation, and this author agrees that many questions remain unanswered, especially when really long-term behavior is to be considered. However, the intense pressures of the weapons test fallout litigations (chapter 12) and other aspects of more dramatic and urgent proportions have siphoned off, at least temporarily, the will and resources to do what really should be done, even though we have the opportunity.

IV. Fission Product Field Releases

The possibility of release of fission products from a nuclear reactor stimulated much interest in gaining knowledge of the fractions of the total inventory that might be released, the chemical and physical form of the released materials, and their potential biological effects. We have already encountered many aspects of this problem. There were reasons to expect that many of them might differ appreciably from the fission products in fallout from weapons tests, especially worldwide fallout. Some of the potential contrasts were pointed out in earlier chapters (e.g., chapters 10, 11, 12). Yet, the newly developing nuclear industry could hardly be expected to do more than calculate. A staged melt-down of a complex and fully instrumented reactor could hardly be counted upon! Luckily, the same question arose in connection with plans for development of a nuclear powered aircraft. The U.S. Air Force went far enough with plans for such a development that they determined that some sort of field studies had to be done. These provided some of the types of data needed in the broader context.

Under the aegis of the Air Force Special Weapons Project, and as part of the "Aircraft Nuclear Propulsion Project," tests were planned with objectives broadly similar to those of the plutonium safety shots we have just reviewed. These were handled largely through the Air Research and Development Command at Kirtland Air Force Base at Albuquerque, New Mexico, and its contractors. There was particular collaboration from the General Electric Company for fuel element and hot-cell aspects; the University of Rochester for biological work; the Idaho Operations Office of the AEC for meteorology, health physics control and site survey, and ecological sampling; the Air Force Special Weapons Center for many logistic and specialized functions; and Convair-Fort Worth. It was determined that the most reasonably realistic surrogate for a potential accident involving an operating reactor propelling an aircraft was to melt down fuel elements and release their contained fission products under known conditions. Questions asked were: (1) release percentages, (2) particle size and size distribution, (3) atmospheric diffusion, (4) deposition on a variety of surfaces, and (5) uptake by living animals and plants, including possible biological effects.

The tests took place primarily at the AEC's National Reactor Testing Station near Idaho Falls, Idaho, but a few were conducted at the Dugway Proving Grounds in Utah. Convair-Fort Worth, the potential builder of a nuclear-powered aircraft, conducted the tests physically under direction of the Air

Force. The role of the University of Rochester was much as it was for the plutonium work. A fairly elaborate set of facilities for animals and biological work was built at Idaho Falls. All biological aspects, except certain ecological measurements, were the responsibility of the Rochester group. R. H. Wilson and R. G. Thomas were again key planners and operators for the biological program. They were joined by R. Lie and G. A. Smith from Rochester; B. B. Boecker, Rochester and later Air Force and Convair-Fort Worth; J. L. Terry from the Air Force; and L. J. Signeur who did behind-the-scenes work. Very satisfactory facilities were developed by modification of three standard Air Force truck trailers. Since these represent something of a climax in the development of such field facilities for biological work and they were very versatile, interior views of the laboratory and animal trailers are shown as figure 14.3A and B.^(a)

These tests were performed in the period July-October 1958. Unlike the work with plutonium, data for the total activity of fission products, the gamma spectra, and, to a degree, the apportionment of activity among the various elements could be determined relatively quickly. Indeed, the results of one test could be used to modify plans for subsequent tests. Also, unlike the work with plutonium, many variables could be introduced in the series and multiple tests accomplished. Besides meteorological conditions, the age of the fuel element, i.e., "green" or "aged" according to the time in the reactor, was a prime variable.

The exposures were carried out by fast melting of the fuel elements from a reactor in a special induction furnace at ground zero. The plume migrated down and across an array of air sampling instruments and animals (animals were not used in all tests). A plume of visible smoke was released immediately preceding and following the fission product release and the plume photographed by ground and aerial cameras. Also, a fluorescent nonradioactive tracer was released to simulate and measure the dispersal characteristics.

The reports of the biological aspects of this work are, primarily, three University of Rochester Atomic Energy Project reports entitled, respectively, *Field Studies of Fission Product Inhalation Parts I, II, and III* (Thomas et al. 1959; Wilson 1959; Thomas and Wilson 1959) and two large reports from the Air Force Special Weapons Center (ANP 1959, 1960). However, there were also Idaho Operations Office reports that gave full details of the physical phenomena (see, e.g., Bunch 1966).

These were relatively short-term experiments. The endpoint, both biologically and physically, was deposition. Few data extend beyond ten days after the release except for two dogs that were placed in metabolism cages and followed for fifty days, and there were some data on tissue content at 150 days or more. Major emphasis was placed on initial deposition and, thus, rapid retrieval of the animals from the field. Evidently the meteorological conditions were sufficiently reliable for the first Fission Product Field Release Test (FPFRT) that no special efforts were needed to provide for quick movement of the animals, as we saw in Operation Roller Coaster. Thus, the array was fixed within a sixty-degree sector, and experimental arcs were at 100, 200, 400, 800, 1,600, and 3,200 m and about 5 mi downwind of the release point. Animals were placed at the

(a) These trailers met their purposes so well that they served for several years as additional (and isolated) laboratory space behind the University of Rochester Atomic Energy Project.



FIGURE 14.3A. (Left) Interior view of trailer utilized for laboratory work, particularly radioactivity counting in the Fission Product Field Release Tests at the National Reactor Testing Station at Idaho Falls. (Courtesy of Wilson 1959.)

FIGURE 14.3B. (Right) Interior view, showing full length of animal trailer used in the Fission Product Field Release Tests at the National Reactor Testing Station. Beyond the dog cages at the far end is a furnace-air-conditioner, water heater and storage facilities. Normally cages for rats were mounted on the right wall. (The usual practice of not mixing species in animal care facilities was not employed because of the relatively short duration of the experiments.) (Courtesy of Wilson 1959.)



100-, 200-, 400- and 800-m stations and as close as possible to the air sampling instruments for those locations. The animals were white rats and mongrel dogs.^(a)

In subsequent operations, a track of perforated steel was laid down, and the animals were placed in wagons that could be moved by pulling on long ropes. This was indeed a prelude to the procedure used at Operation Roller Coaster.

Despite the predictions from experience, the first tests in the fission product release series were done without special precautions to minimize ingestion of materials deposited on the fur or around the noses of the animals.

In the trials with rabbits, reported in the Aircraft Nuclear Propulsion report (ANP 1959), scalp activity and lung activity were reported. In general, they correlated well with each other with distance from the shot release. In the early Rochester experiments, the animals were in open cages, and deposition in the gastrointestinal tract was unrealistically high. Alteration of the exposure cage design to minimize licking of the fur, anesthetizing the animals, and changing the methods of sacrifice brought the gastrointestinal-tract-to-lung ratios from more than thirty to one to less than one to one. However, care had to be exercised not to alter significantly the respiratory functions of the animals, and anesthesia was not used routinely. Changes in the contours of the exposure cages (primarily those for the rats), muzzling the dogs, and great care not to introduce artifacts at the time of collection were the most useful ways to avoid unwanted ingestion of the fission products. The nuances of these and other details of methodology are described by Thomas et al. (1959) and Wilson (1959).^(b)

It turned out that the "aged" fuel elements released an aerosol composed primarily of cesium. Indeed, about 83% of the premelt cesium was lost from the elements. Counting and dose calculations were relatively easy. The "green" fuel elements produced more of a mixture, but iodine predominated. In fact, the results were routinely reported in two parts, iodine and all other isotopes. The latter category had a half-life greater than thirty days. It was inferred that the iodine was largely in an uncombined form. Another difference between the two forms of elements was seen in the ratio of external contamination to lung. For the releases from green elements, this ratio (for iodine) was ten times that seen for cesium from the aged fuel elements. Thus, a difference in physico-chemical properties (solubility?) undoubtedly existed. For these reasons, the results for the two forms of elements were reported separately.

Deposition (median) in the lower respiratory tract of rats and dogs is summarized in the following data modified from Thomas et al. (1959):

aged elements:	green elements:
54 rats = 28%	116 rats = 33%
12 dogs = 24%	18 dogs = 35%

On this basis, the combined figure for deposition in rats was taken as 33% and for dogs 31%. What is not shown is the rather large range of variation of the figures. Nevertheless, the median figure for deposition in the lower respiratory

(a) Some of the ANP documents mention rabbits for some of the early tests. It is not clear who had responsibility for these, presumably not the University of Rochester. They appear to have been used only for measurements of external contamination. (Wilson [1984] suggests that this refers to the numerous indigenous jack rabbits.)

(b) The first test described by Thomas et al. (1959) released so little activity that no conclusions could be drawn.

tract was not seriously at odds with the usual figure, 25%, derived from the then-extant lung model (see chapter 16). Total deposition, i.e., deposition in (and on?) the whole animal, showed a median of 67% without much difference between aged or green fuel elements. For several reasons, the authors preferred to utilize a total deposition figure of 75% for hazard-evaluation purposes.

Tissues were analyzed in some instances for periods up to over 150 days after exposure. In addition to gastrointestinal tract (sometimes done in segments), lung, kidney, muscle, and blood were analyzed (the latter only when samples of 120 ml or more were available). The results are outlined below:

1. In the work with green fuel elements, stomach appeared to contain much more iodine than any other portion of the gastrointestinal tract or any other organ. The ratio of iodine to long-lived fission products was about three for kidney, lung, and small and large intestine, but it was about nine for stomach. Air-filter samples were like all organs except stomach. Thus, some selective accumulation in stomach must be considered.
2. Lung contents (total count) fell considerably less rapidly with time than did stomach, while kidney and lung were roughly comparable.
3. The time course and element ratios on the average air filter and in lung were roughly comparable.
4. Esophagus was high compared to lung or gastrointestinal tract after exposure to the aged fuel elements.
5. There was essentially no cesium in muscle, even from experiments with the aged-fuel-element release.
6. In general, radionuclides from the aged elements, e.g., cesium, were more slowly transported than those from the green elements, e.g., iodine.
7. Thyroid uptake was analyzed in some of the dogs, but only after *intravenous* injection.

The two dogs placed in metabolism cages for fifty days showed unexpectedly almost equal amounts of gross activity in urine and feces over the entire fifty-day period. This indicates the presence of insoluble radioactive material in the lung that was being gradually fed to the gastrointestinal tract by pulmonary clearance processes. Since the exposure came from what was considered a green fuel element, this implies that the mobile iodine was not the only element present.

The work at Dugway is described in the second Convair report (ANP 1960). The fallout patterns at Dugway are described therein for eleven releases using fuel elements of the type planned for the ANP reactor. Exposure of animals is indicated as having taken place, and the statement is made that the results would be reported by the University of Rochester. However, no such reports appeared. It is understood (personal communications from the Rochester group) that the biomedical data obtained could not be used.

The purpose of these tests was hazard evaluation. What was found that might modify analyses of hazard derived from laboratory experiments?

1. The age of the fuel elements makes an obvious difference in the elements of importance. This could have been determined from the laboratory work. However, the difference by a factor of ten in deposition velocity could not have been guessed.
2. The constancy of urinary to fecal excretion rates, seen in the metabolism dogs, was not expected.

3. Gross fallout measurements can give misleading results for estimation of body (i.e., lung) uptake. Individual elements must be considered in part.

Unfortunately, the number of animals in this work is small, and ranges of variation are large. A larger series might have made the conclusions more certain. Nevertheless, the work was a worthwhile check of field versus laboratory with, as in other cases, significant differences noted.

In a broader sense, it may be asked if these biomedical tests discouraged the further development of the nuclear-powered aircraft, particularly from the standpoint of potential environmental contamination. This seems unlikely. It is true that the longer-lived fission products could assume greater importance in the operation of such devices than in fallout from weapons tests. Yet, nothing in the reported results indicated the presence of problems so drastically different from the predictions that the project should be discontinued. It seems more likely that protection of the crews by shielding and by wide separation from the reactors presented more serious biomedical problems than those of environmental contamination. Nevertheless, the public reaction to a device that had to discharge some fission products to the atmosphere in normal operation and that could not be made heavy enough to contain, for certain, the enormous radioactive inventory in the event of an accident was likely to be quite negative. Very real advantages, even over and above the potential for very long flight times, had to present themselves.

In any event, the ANP project wound down, and there were no more biomedical tests. There were, however, related ones in the projects Kiwi, etc., as we reviewed in chapter 9 and will consider again briefly later in this chapter.

V. Project Plowshare

A. Development of the Plan

Project Plowshare was one of the most ambitious and extensive facets of the Atoms for Peace Program.^(a) It envisioned the use of nuclear explosives for relatively quick and inexpensive (in comparison to conventional means) digging of harbors; for releasing large stores of natural gas or petroleum trapped underground in impermeable strata; for transportation construction projects requiring the "moving of mountains"; waterways; even to the digging of a new canal from the Atlantic to the Pacific across the isthmus of Panama or adjacent thereto.^(b) It was a visionary project built around Isaiah's ancient prophecy, "and they shall beat their swords into plowshares."

Several books were written directly about the ideas of Project Plowshare. Two are cited for the reader's convenience: a semipopular description by Ralph Sanders, Washington, D.C., with a foreword by former AEC Commissioner Willard F. Libby (Sanders 1962), and a more technical treatise by Edward Teller and collaborators (Teller et al. 1968). There were, in addition, many special

(a) See especially chapter 20 and references given therein, as well as passing mentions in other chapters for description of the Atoms for Peace program and its origins.

(b) Other possible uses were in mining; the production of power by utilizing the long-lasting heat from a nuclear detonation in deep rock; the production of isotopes and of chemicals that could be extracted; and various scientific applications pertinent to neutron physics, geophysics, and space physics.

symposia on all aspects of the project. The Lawrence Livermore Laboratory of the AEC was founded largely because of the anticipated needs of Project Plowshare and was called upon for broadly based inspiration and guidance, as well as much labor. Consequently, a large number of Livermore reports pertain to the various aspects of the Plowshare Project. The AEC issued a booklet devoted to Plowshare in its information series, "Understanding the Atom" (Gerber, Hamburger, and Hull 1967).

These ideas were, of course, not a U.S. monopoly. Several countries showed interest and formulated plans. The Soviets not only had interest but are reported to have actually carried out some real projects, not just tests (Sanders 1962, references for chapter IX "The Soviet Stake"). There is no doubt that many of Russia's water problems might be susceptible to the enormous energies of nuclear explosives. Scheimer and Borg (1984) describe deep seismic sounding with nuclear explosives in the Soviet Union. Also, fairly recent newspaper stories (*San Diego Union*, Associated Press 1984) describe proposals to build a long-dreamed-of canal between the Indian and Pacific Oceans across Thailand's Kra Isthmus. Thus, the ideas are still viable.

B. Operations

A total of twenty-seven of the announced nuclear tests carried out by the United States (see chapter 12) were labeled as "Plowshare Events." These ranged from much less than a kiloton to over one hundred kilotons, largely underground or, at most, cratering events. Most were at NTS, but there were special events in Colorado and New Mexico. They occurred over the period December 1961 to May 1973. We will have reason to cite specifics concerning a few of them as we proceed.

Only a few of the twenty-seven shots had overt biomedical components. Most of this consisted of follow-up of fauna and flora in the craters produced or exposure of living organisms to the radioactive debris derived from the sites. One (the Sedan event) included placement of some animals by Placak's group for the PHS (Wilson 1984), but results seem not to be available. All had components of hazard evaluation, and for some this became a central feature.

A large effort was expended by the biomedical community in calculations of the potential doses to humans from radioactivity that might be released in large "geographical engineering" events. Principal among these were dose-estimation studies related to a possible Atlantic-Pacific Interoceanic Canal. While the overt cratering events were monitored by personnel from several laboratories, this computational work resided primarily at ORNL, Health Physics Division and Environmental Sciences Division, and BCL. Since this computational work had the most direct bearing on radionuclide problems, we will examine it first.

C. A New Interoceanic Canal—The Computational Approach

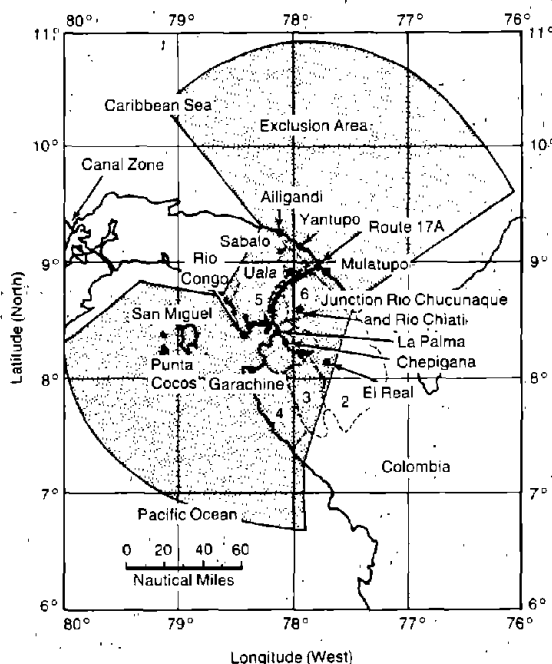
The idea of producing a sea-level canal by detonating rows of buried nuclear charges was consolidated into the Atlantic-Pacific Interoceanic Commission. With the internal dosimetry group at Oak Ridge already deeply involved in computer calculations for revisions of standards for exposure to radioisotopes being considered by bodies such as ICRP, the National Council on Radiation Protection and Measurements (NCRP), and the Medical Internal Radiation Dose [Committee of the Society for Nuclear Medicine] (MIRD) (see chapters 16

and 20); it was logical to ask them to expand further into population exposure standards. This resulted in a series of reports organized by Walter Snyder and carried on by his colleagues.

Tied closely to this work was that at BCL for provision of some of the potential source terms ($\mu\text{Ci}/\text{cm}^2$ of land surface and $\mu\text{Ci}/\text{day}$ intakes)^(a) and judgments to determine, on the basis of the ORNL and other analyses, if the nuclear excavation plan could be carried out safely. For this they used comparisons of the predicted doses to established radiation safety standards for populations.

Many potential routes for the canal were considered. The BCL personnel, the Puerto Rico Nuclear Center (particularly Frank Lowman), and PNL conducted onsite research in Panama and Colombia to check out the pros and cons of each route. By contrast, the ORNL calculations concentrated on only the two most promising routes: Route 17 through the Darien region of Panama and Route 25 across North-eastern Colombia. These are mapped in figure 14.4A and B. For each route, a combination of nuclear and high-explosive events was planned. This was taken into account in the dosage calculations.

FIGURE 14.4A. Map of Panama illustrating the Route 17 alignment, watersheds (numbered), and locations of towns and villages for estimates of external dose. (Redrawn from Kaye and Rohwer 1970.)



In-depth presentations of the enormous effort needed for the dosimetric calculations are given in three ORNL reports: Cowser et al. (1967); Turner, Kaye, and Rohwer (1968); and Kaye and Rohwer (1970). The objectives were estimation of potential radiation doses to humans, comparison of these to existing radiation protection guides, and recommendations to limit potential radiation doses to the lowest practicable levels. The three phases, which covered the periods July to December 1966, January 1967 to June 1968, and July 1968 to June 1970, respectively, are described as follows.

(a) Many additional input factors were worked out by ORNL.

FIGURE 14.4B. Map of Colombia illustrating the Route 25 alignment and watersheds (numbered). (Redrawn from Kaye and Rohwer 1970.)

Phase I—Quantification of transfer of radionuclides through critical exposure pathways, identification of critical radionuclides, criteria for evaluating radiological safety of nuclear excavation, and lists of radionuclides in order of external or internal exposure capabilities.

Phase II—Development of computer codes for estimating internal and external radiation doses under the conditions and modes of exposure expected to be important. Both the specific-activity and environmental-systems-analysis approaches were tested.

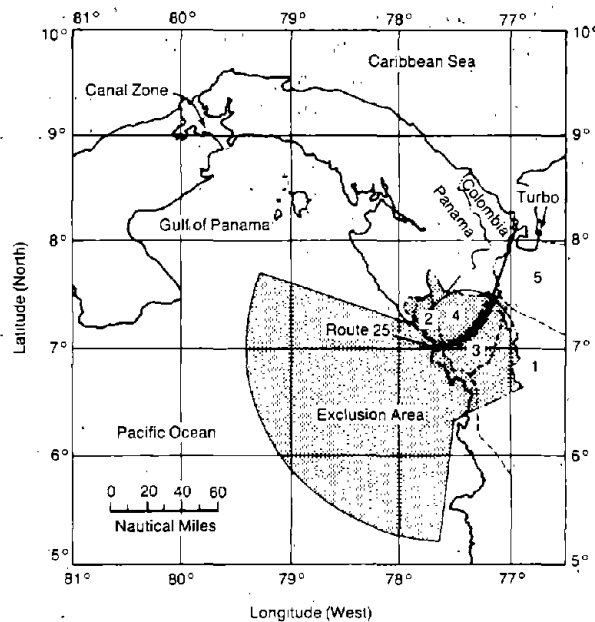
Phase III—Final estimates of potential doses, their assessment and formulation of recommendations.

We can summarize the results of each phase by reproducing the abstract from each document below:

Abstract of Phase I—This report presents information obtained by ORNL in Phase I of dose-estimation studies to evaluate the radiological-safety feasibility of excavating an Atlantic-Pacific interoceanic canal with nuclear explosives. The information includes (1) methods for estimating external and internal dose equivalents, for quantifying the transfer of radionuclides through critical exposure pathways, and for identifying the radionuclides likely to be critical; (2) criteria for evaluating the radiological safety of the operation; and (3) lists of radionuclides arranged according to the dose commitment that results from exposure to a unit quantity of each radionuclide. Equations to estimate external and internal radiation dose commitments were developed which account for production, venting, and movement of radionuclides in environmental exposure pathways. A compartment model for representing movement of radionuclides in the tropical environment was designed with coupled compartments having income and loss fluxes controlling the inventory of radionuclides which may have inputs to man. The specific activity concept for estimating the allowable radionuclide concentrations in the environment was evaluated in a way that reveals its limitations, considering the time-dependent relative importance of radioactive half-life, biological half-time, and biological growth.

Criteria for evaluating radiological safety were developed from the recommendations of recognized authorities which might reasonably apply in an operation of this magnitude, taking account of the principle of balancing the possible benefits against the potential risks.

(Cowser et al. 1967)



Abstract of Phase II—EXREM is a computer code to estimate the dose equivalent rate and the total dose equivalent from both beta and gamma radiation resulting from submersion in contaminated water, submersion in contaminated air, and exposure to a contaminated surface. There can be more than one environmental release, and exposure can begin at any time after the first release. INREM is a computer code to estimate the cumulative dose equivalent to body organs resulting from a continuous intake. The organ parameters are dependent on the age of the individual, and the intake is a function of post-detonation time and the individual's age.

Although the codes were specifically written to estimate doses to populations from construction of a sea-level canal, they may be useful in other dose-estimation studies involving releases of radioactive materials to the environment. (Turner, Kaye, and Rohwer 1968)

Abstract of Phase III—This document is the final report covering contributions of the Health Physics Division of Oak Ridge National Laboratory (ORNL) to the Bioenvironmental Radiological Safety-Feasibility Study of a sea-level canal excavated with nuclear explosives. Potential doses to indigenous populations along Route 17 in eastern Panama and Route 25 in northwestern Colombia were estimated for a combination of hypothetical exposures to radiation. The studies attempted to determine when it might be appropriate for the evacuated populations to reenter areas adjacent to the two routes. The only modes of exposure considered were external exposure to a contaminated land surface and internal exposure from the ingestion of four types of contaminated foods and beverages. Parameters in the internal dose models were adjusted to differentiate five age groups within each of four indigenous populations and nine reference organs. These populations were further differentiated on the basis of diet and estimates of time- and age-dependent concentrations of radioactivity in dietary items. Intake functions (μCi ingested per day) for internal dose estimates were average values for watersheds with the highest initial areal concentration of fallout along each route, whereas external doses were computed for 13 locations (towns and villages) in watersheds of the exclusion zone of Route 17 only. Estimates of potential external doses were based on 170 radionuclides; only 31 radionuclides were considered in detail for the estimation of potential internal doses, with an approximate estimate of total dose from the radionuclides not included in the list of 31.

Estimates of potential total doses (internal dose from ingestion + external dose from land surface) were assessed in terms of radiation safety criteria recommended for members of the public by recognized authorities. The basic criteria were: annual dose limit for the total body of 0.17 rem/year and a genetic dose limit of 5 rem/30 years. Assessments based on somatic doses suggest reentry may be appropriate 8 to 10 years after the last detonation. Children less than 5 years of age at the time of reentry may be the critical age group among the age groups for which doses were estimated. Within this age group, no single ethnic group emerged as the most critical. Assessments based on genetic dose appear to be less limiting, suggesting that reentry may be possible within months following the last detonation. These assessments are based on comparisons with the total doses allowed under the radiation safety criteria. In actual practice, however, some apportionment of these criteria might be likely. Such an apportionment should be undertaken by the countries involved (Panama and Colombia). (Kaye and Rohwer 1970)

These abstracts, particularly the one from the Phase III report, give figures for safe re-entry, as we see, from eight to ten years, based on somatic dose. These would create the impression that some final conclusions had been reached and that the projections were unlikely to be acceptable. Any project that would require such long waiting periods for return to full-time habitation

and temporary domicile elsewhere under conditions that would be far from ideal was hardly one to gain much support, particularly for populations of countries with a relatively small stake in the project. This would hold even if the exclusion area gradually narrowed down to a mile or two from the excavation site. (The cratering shots at NTS showed that most of the radioactivity was in the material actually thrown out of the crater and did not extend very far except for the initial cloud.)

Reading further into the detailed discussion, we find that the authors of the Oak Ridge reports concluded that they could not provide a definitive assessment of radiological safety with the information at hand. Three potentially important routes of exposure were not included in the studies: submersion in air, submersion in water, and inhalation.^(a) Furthermore, the parameters for humans and the environment were not only numerous but had to be based upon data using Standard Man^(b) and environmental practices in North America and Europe, not the ethnic groups or agricultural practices of Central America. The authors recommended stable element analyses of total diet and total excreta in the areas of interest for the canal; measurements of organ weights, dimensions and stable element contents using cadavers; direct determination of intercompartmental transfer functions in the tropical ecosystems involved; etc.

It is hard for this author to see how gathering such information, and it would require a large research effort, could alter the conclusions sufficiently to make the project look really attractive. Yet, he must agree with the authors when they say, "For a project of this magnitude and potential impact, educated guesses or unfounded assumptions are not a satisfactory substitute for real data, especially when it is technically and economically feasible to procure the necessary data on which a realistic assessment could be made" (Kaye and Rohwer 1970, p. 98).

On the other hand, the study appears not to have uncovered radiological problems that could not be managed by "adequate planning and reasonable precautions," some of them quite demanding, even drastic, except for one unknown. The large amounts of radioactivity trapped at or below the bottom of the proposed canal could not be counted upon to remain there indefinitely. Yet, models for the behavior of this component seemed especially difficult to construct.

Despite the fact that the answers could hardly be expected to generate unbridled enthusiasm for the canal project, the work served many useful purposes. It developed an approach to evaluation of environmental and population exposures that had much greater flexibility and versatility than the old system of MPCs. It went far along the path of identifying and isolating critical processes, critical populations, and critical radionuclides. Its usefulness went far beyond the calculation of potential radiological safety in Project Plowshare. Glimpses of this can be seen in the open literature publication by Kaye et al. (1969).

For example, the work led to the development of a generalized exposure index system called CUEX (Cumulative Exposure Index) and fed much information and technique into the ongoing work of ICRP, NCRP, the Nuclear Regulatory Commission, and the federal establishment in general. These will be

(a) The open literature publication by Kaye et al. 1969 appears to include these:

(b) For example, the internal dose parameters used for the INREM code were Standard Man values or modifications thereof.

discussed briefly in chapter 16. The CUMEX program will be described in chapter 15, since it pertains more to environmental transport problems, in general, than to Project Plowshare alone.

The computational approach in the enormous effort described above was largely a systems-analysis approach. In earlier discussions, we mentioned that a specific-activity approach had been applied to environmental dose assessments. The Oak Ridge people took pains to present a formal discussion of this approach, particularly since it was suggested by the National Academy of Sciences-National Research Council committee on Oceanography and Fisheries, as described in chapter 11.^(a) Kaye and Nelson presented a concise analysis of the specific-activity concept as related to environmental concentrations of radionuclides, with the conclusion that bioengineering of the proposed Inter-oceanic Canal could be approached through the specific-activity method as well as others' (Kaye and Nelson 1968). The major problem with the approach is incomplete mixing of the stable and radioactive isotopes and potential differing biological availability of the stable and radioactive components—not minor problems.

These computations for Project Plowshare obviously contributed considerably to the progress of internal emitter dosimetry. When one considers the hundreds of nuclides examined, their ranking according to their importance in each of several intake patterns, and the exhaustive analyses of the environmental transfer processes (to be discussed in chapter 15), this conclusion is amply supported. Nevertheless, attention gradually moved toward other applications. First we must look at the types of biomedical work done in connection with the cratering tests.

D. The Cratering Events

Of the twenty-seven special nuclear explosions labeled as Plowshare shots, all but five took place in underground shafts or tunnels. These five exceptions took place at NTS. One of the most spectacular, as well as one of the earlier shots, was the "Sedan" shot. A 104-kt device was exploded 635 ft below the surface on July 6, 1962. (This had been preceded by several smaller cratering experiments. One of the objectives was to test the validity of the scaling laws developed.) The shot excavated a crater 1,200 ft in diameter, and 320 ft deep, and it moved a volume of 6.5 million cubic yards of desert alluvium. A picture of this awesome cavity is shown as figure 14.5.

Most of the radioactivity was deposited nearby, but appreciable amounts of fallout with external dosage of over 0.5 R infinite dose were carried for up to one hundred miles. A diagram of the fallout pattern is seen in figure 14.6.

Note that the contours given are for the infinite dose and also that the technology between 1962 and 1965 improved considerably and was postulated to improve still further with future developments. However, we have heard little more about these.

Other pertinent cratering events were Cabriole, Buggy, and Schooner. These had lower yields, viz., 2.3 kt, 5.4 kt, and 30 kt, respectively. The last announced cratering event took place in December 1968.

(a) Remember, too, that the concept was applied by the Oak Ridge group to clams and clam shells and ^{90}Sr in the Tennessee River system.

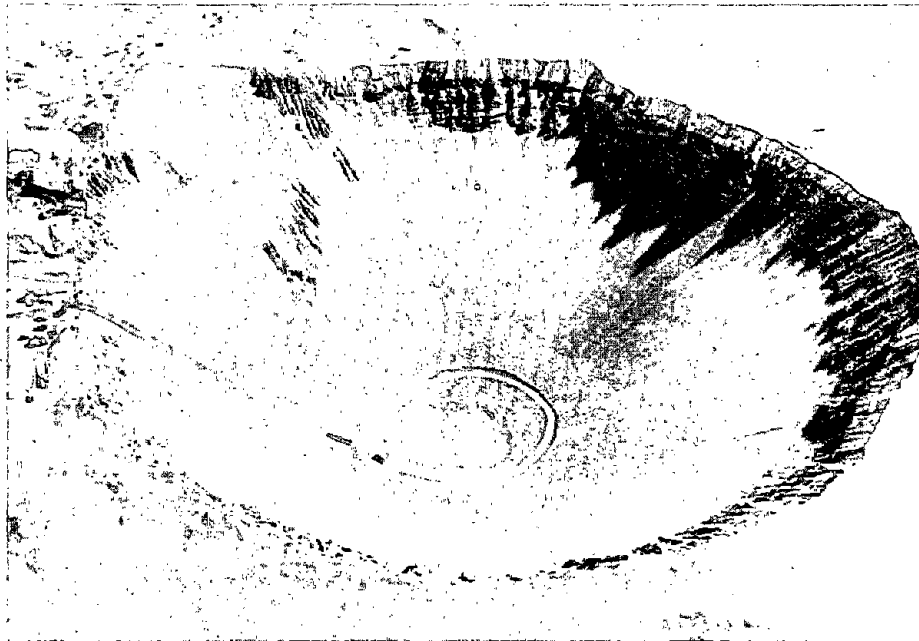


FIGURE 14.5. The 100-kiloton Sedan event formed the largest excavation ever produced by a single manmade explosion. Note the size of automobiles and structures near the crater's rim. (Courtesy of Gerber, Hamburger, and Hull 1967, p. 34.)

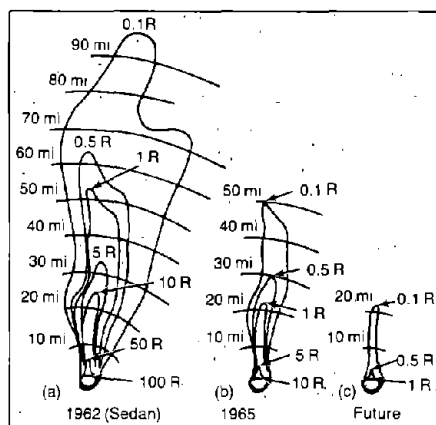


FIGURE 14.6. The radioactivity escaping from a nuclear excavation depends both on the total amount produced by the explosion and the fraction that escapes into the atmosphere. The diagram on the left shows the pattern of the fallout that was observed in 1962 from the 100-kiloton Sedan experiment. The center pattern indicates the fallout that might have been expected if Sedan had been conducted with 1965 technology. Explosives development and improvements in emplacement techniques are expected to reduce the radioactivity released from nuclear excavations to that shown in the right-hand drawing. The decrease from the left-hand to the

right-hand pattern is about a hundredfold. The amount of radioactivity released is relatively independent of the size of the explosion. These fallout patterns, shown in terms of infinite dose, indicate the dose of external gamma radiation that a person living outdoors for a lifetime might receive at various distances from the excavation. For comparison, the average external gamma dose a person in the United States receives from natural sources of radiation is about 0.1 roentgen (R) per year. (Redrawn from Gerber, Hamburger, and Hull 1967, p. 19.)

Biomedical work in general around these cratering events consisted of, in addition to the monitoring and dosage estimations, examination of flora and fauna from within and around the sites. This was aimed primarily at identifying the radionuclides present and gauging their mobility in the biosphere. Particular interest centered on the radionuclide species induced by the large neutron fluxes. The work was done largely by the groups at LLL and UCLA. Some of the work was in the field, some of it brought the contaminated soil to the laboratory for work under more controlled conditions. Typical examples are: (1) for Project Sedan, the neutron activation products in plants and soils (Romney and Rhoads 1966)^(a) and concentrations of radionuclides in plants grown in ejecta from Sedan (Romney et al. 1967 and a report on beagles at Project Sedan [Fountain 1963]); (2) availability to aquatic animals of short-lived radionuclides from the Cabriole event (Harrison 1973); and (3) availability of radionuclides from the Buggy cratering event to the peccary pig, and to the domestic pig from Project Schooner (Chertok and Lake 1971a,b).^(b)

There was also a series of UCLA reports and reports in the Plowshare series concerning additional biomedical studies of the Sedan test. These considered effects on close-in vegetation, direct effects (Martin 1963), food-chain relationships of radioiodine (Turner and Martin 1964), and of radiostrontium (Martin and Turner 1965); also a "final" report concerning movement of radionuclides in soil (Essington, Nishita, and Steen undated). There was also work on the population of lizards at Project Sedan (Turner 1963). All of this work is replete with modeling and undoubtedly contributed to the input data utilized by BCL in the computations described in section C.

The Sedan products were found from both laboratory and field experiments to contain so much tungsten that the investigators concluded it had been incorporated in the device. There were considerable differences in the way different nuclides were handled. Some concentrated more in leaves than stems, some vice versa. Plant uptake was influenced quite considerably by the type of soil, as we saw in chapter 13.

The work with the Cabriole soil was done in the laboratory by circulating aquarium water through a column containing the ejected soil. The main potential contributors to humans from either freshwater or marine animals were ^{131}I , ^{140}Ba / ^{140}La , and ^{185}W .^(c)

The work with the peccary pig was also in the laboratory. Two pigs were given single oral doses of the fallout from Project Buggy, the fallout having been collected on a tray about 1,000 ft from the detonation. Urinary and fecal excretion were measured and gut absorption calculated. Only iodine was absorbed to any significant extent. Again, some unfamiliar radioisotopes appeared in the cadre.

There was also work concerning the distribution of radionuclides in ground water after underground explosions like those in the Plowshare series (Stead 1964).

It was clear from all of this that the inventory of radioisotopes could vary with the shot; partly because of the circumstances of the event and partly because weapons designers manipulated the contents of the devices to meet their own purposes. Fortunately, these did not make serious problems for the biomedical

(a) This followed an earlier report on the fission products found in Project Sedan soil.

(b) The first work was one among many from UCLA; the others were part of the work at LLL.

(c) Note that this line-up is somewhat different from that seen with fallout from weapons.

evaluations, although there is no doubt that the order of elements might be changed in computations such as those described in section C. Also, fortunately, the key "bad actors" seemed to remain pretty much the same, despite the differences in details of the events.

E. Gas Stimulation Experiments

One of the more carefully tested ideas in the Plowshare domain was the use of nuclear explosives to release natural gas from impermeable strata. It has been estimated that trillions of cubic feet of natural gas are impounded in the earth below and within strata that are impermeable to either gas or oil. As described in the general references (Sanders 1962; Teller et al. 1968), nuclear explosives seemed especially adapted to tapping some of these resources. The enormous heat and fracturing of large areas of rock were considered strong plus values over the release by chemical explosives, a process already tried and known to be successful, but on too small a scale. However, the gas so stimulated could not help but contain measurable, perhaps even hazardous, quantities of radioactivity. Thus, tests done to see if stimulation could be brought about included fairly elaborate procedures to check total radioactivity released, to identify the radionuclides likely to be of the greatest importance, and to make judgments concerning the possible hazards of use of such gas under commercial and domestic conditions. One of the tests even resulted in litigation and a court judgment on the hazards.

There were three fracturing experiments,^(a) all officially part of Project Plowshare and each a joint U.S. government-industry cooperative venture. Project Gasbuggy involved a 29-kt device exploded in strata near Farmington, New Mexico; it took place in 1967. Project Rulison involved a 40-kt underground (shaft) detonation near Rifle, Colorado, in September 1969. The final test, Project Rio Blanco, took place near Meeker, Colorado, in May 1973. This involved three separate 30-kt devices in the same borehole at depths of 1,779; 1,899; and 2,039 m below the surface. Each site was, of course, chosen to be suitably isolated yet approachable and in formations where gas was expected to be available for stimulation. The stimulation was successful in each case.

It was decided from the outset that none of the released gas would be put into commercial or domestic mains. Yet, the necessary biomedical and other information could not be obtained without burning the gas in some way. Also, the gas could not be released safely to the environment without burning. Thus, it was decided to engage in periodic flaring of the effluent. The meteorologists and aerosol scientists found much to measure during these flaring events. We will sample the biomedical work.

In connection with Project Gasbuggy, investigators from the EPA laboratories in Las Vegas (Mason et al. 1971) soon identified the primary radioactive component of the gas, from the standpoint of hazard, to be tritium. They measured its uptake, largely as tritium water, by desert vegetation. This was done by extracting and measuring the tritiated water from vegetation samples. The amounts ranged from well below to factors of ten or more above background,^(b)

(a) So called because the prime interest was fracturing of the impermeable rock strata.

(b) For technical reasons, background was not determined for plants on the site prior to flaring. Instead, a background level for tritium in vegetation was estimated from samples collected independently over portions of Arizona, Colorado, and New Mexico.

depending upon location with relation to the stack and micrometeorology of each sampling location. The primary conclusions related to technique and the testing of various equations for movement of small air masses over rugged terrain, but they also addressed the best way to express tritium concentration in such samples. It was decided that for some purposes specific activity was best, for others the concentration on the basis of dry weight was best. It was recommended that both be used.

A thorough analysis of radioecological processes at Project Rulison was presented by the LLL people at the Third National Symposium on Radioecology (Anspaugh, Koranda, and Robison 1971). Their findings, which incidentally mentioned that successful development of the nuclear gas stimulation technology could double the proven recoverable natural gas resources in the United States, were a clear example of the need for such tests. Concentrating on releases of tritium, as THO (or HTO), they found that the environmental residence time of HTO is at least an order of magnitude shorter than was projected by computations.^(a) This in turn invalidated the deposition-velocity approach for the calculation of doses due to food-chain contamination.

On the basis of the actual data, the LLL investigators developed new models to predict the dose to humans via forage-cow-milk, forage-cattle-beef, vegetation, and inhalation pathways for HTO, and immersion dose for ^{85}Kr . All of these were based on flaring of the gas according to predetermined schedules. An upper limit of 3×10^{-6} rem to the Rulison residents was determined, which is between three and four orders of magnitude lower than preflaring estimates by several organizations, including LLL itself (Robison and Anspaugh 1969).

An attempt was made to verify the model by environmental samples, even though most of them had to be expected to be below detection limits. The EPA collected twenty urine samples from local residents, seven animal, eight milk, and fourteen vegetation samples (Gotchy 1971; Carter 1971). Only four samples, all of them vegetation, were above background (about 1 pCi/ml). Anspaugh also collected vegetation and milk, but no samples contained tritium levels above background.

Anspaugh et al. extrapolated the Rulison calculations to large-scale uses. If natural gas with 1 pCi of tritium/cm³ of gas were used to replace natural gas for heating and cooking in the Los Angeles or San Francisco Bay area, the dose to users by inhalation and absorption would be about 5×10^{-3} rem/yr. It would be 2.1×10^{-4} rem/yr to infants by all pathways if the stimulated natural gas were used to produce electricity instead of directly for heating or cooking.

Somewhat later, the Oak Ridge group (Health Physics and Environmental Sciences Divisions) evaluated all three gas stimulation experiments. Although the inventory contained ^3H , ^{14}C , ^{37}Ar , ^{39}Ar , ^{85}Kr , and ^{203}Hg ,^(b) it was computed (Rohwer et al. 1973) that tritium contributed 60% of the somatic dose and 93% of the genetic dose, while ^{85}Kr contributed 39% and 6% of these doses, respectively. They calculated doses to individuals resulting from combustion of the gas in unvented home appliances as less than 20 mrem/yr. Since most U.S. cities and states require venting of gas appliances, except cooking stoves, this figure is clearly a maximum. If the nuclear-stimulated gas were used for providing electricity, the maximum individual dose was calculated to be 0.006 mrem/yr or,

(a) Laboratory work at Livermore confirmed this finding.

(b) From neutron activation of stable mercury in the rocks.

using a particular station in and the demography of the Denver area, 0.32 man-rem. By contrast, in using the gas directly in the home, making many assumptions about the proportion used for various purposes, the population dose came to about 110 man-rem, or nearly 350 times the population doses accumulated by using the same amount of gas to generate electricity.

Despite this apparently large factor between modes of use, it is clear that the population doses to be expected if natural gas like that from Rulison were used commercially would be, in either situation, very small. Doses from radon and its daughters in indoor air are notably higher (chapter 3, NCRP 1984). Whether or not stimulated natural gas could actually be obtained at average or maximum levels like $1 \text{ pCi } ^3\text{H}/\text{cm}^3$ is not easy to guess. Scaling factors are currently quite crude, and the biomedical and seismic effects of much larger stimulation experiments cannot be judged on a priori grounds. Thus, we must withhold judgment regarding the actual doses that might ensue.

It was the Rulison experiment that became grounds for litigation. It was contended that current radiation protection standards were insufficiently conservative and would not protect life, health, and property if the stimulated gas were released or flared as per plan. A nonjury trial was held in Federal District Court in Denver and heard by Judge Alfred A. Arraj. The details are available in the public record, including the newsletter of the Health Physics Society in 1970. The ruling, which found there was no unacceptable hazard, is an excellent summary of radiation protection philosophy and ideas as they stood at the time. It can only be surmised what the ruling in a similar case might be at present.

Despite the evidences that doses would be low from use of stimulated natural gas, this feature of Plowshare died too. Whether or not the biomedical aspects were a central cause cannot be stated. There were many other factors such as costs, lessening of demand for new domestic supplies of gas, and general public suspicion of anything nuclear.

F. Alaskan Operations

Edward Teller, who can be regarded as at least a patron, if not the father, of many aspects of Plowshare, fostered elaborate plans for a "harbor-digging" (actually a cratering test) along the coast of Alaska. To prepare for such an event, or events, an extensive ecological program was undertaken. This, plus the other planning and feasibility studies, was called "Project Chariot." The biomedical aspects were contained in a large book entitled, *Environment of the Cape Thompson Region, Alaska* (Wilimovsky and Wolfe 1966). A quotation from the foreword for this book gives the purposes and an overview of what was done.

After the consideration of a number of possible locations for the project, a site at the mouth of Ogotoruk Creek near Cape Thompson on the northwestern coast of Alaska was selected for detailed study. Because the project site was in an environment for which there was no prior nuclear test experience and little scientific knowledge of the environment, bioenvironmental investigations in addition to the usual public-safety program were approved to allow adequate assessment of the effect of the proposed project and to assure that it could be conducted safely.

Accordingly, the San Francisco Operations Office, AEC, formed a committee, chaired by a member of the Division of Biology and Medicine, AEC, to develop and recommend a program of environmental studies for Project Chariot. Members of the Committee were selected from a variety of scientific disciplines on the basis of their experience in arctic research or in the effects of nuclear explosions.

In carrying out its assignments, the Committee set the following objectives:

1. To become sufficiently familiar with arctic ecological systems in the project area to permit: (a) estimates of the biological cost of the excavation operation and (b) judgements as to whether or not there would be effects that could result in widespread damage or major disruption of ecological systems.
2. To become sufficiently familiar with the biological and physical environments that the findings could be used as base lines in studies to be conducted in post-excavation time.
3. To determine radiation levels and the distribution of the radioisotopes in the biota and physical environment in pre- and postdetonation time.
4. To conduct all studies in such a manner that the results would constitute a significant contribution to scientific knowledge.

Implementing these objectives, the Committee initiated more than forty separate investigations, conducted primarily during the period 1959-1961. These activities were performed by university, private, and governmental research organizations under contract to, or agreement with, the Atomic Energy Commission.

Since by 1962 much of the desired nuclear-excavation engineering data originally planned to be obtained in Chariot had become available or would be available from other experiments being planned, the Atomic Energy Commission announced that it had decided to defer further consideration of the proposed Chariot experiment. Accordingly, Project Chariot was suspended and the bioenvironmental studies were concluded.

The scientific studies of the Environmental Program, although naturally lacking any postdetonation studies, have been compiled in this volume to present the scientific community with an integrated reference collection of technical papers accruing from the investigations. The breadth of environmental features studied at the Chariot site and in the adjoining area, and their interrelations, will be apparent to the reader of this book.

(Wilimovsky and Wolfe 1966)

The Committee was chaired by John N. Wolfe of the AEC, while Allyn F. Seymour, University of Washington, was deputy chairman.

Major research groups who participated in the Project Chariot field studies included Hanford; University of Washington; U.S. Geological Survey, Menlo Park, California, Denver, Colorado, and Silver Springs, Maryland; U.S. Weather Bureau Research Station, Las Vegas, Nevada; Marine Mammal Biology Laboratory; Bureau of Commercial Fisheries, Seattle, Washington; Arctic Health Research Center; PHS, Anchorage, Alaska; University of Alaska; Scripps Institution of Oceanography; McGill University, Montreal, Quebec; and the University of British Columbia.

These studies were hardly what was in mind when the original plans were laid to carry out a full harbor-digging operation under Project Plowshare. On the other hand, the basic information obtained regarding the undisturbed arctic environment was unique and voluminous and is contained in the Cape Thompson compendium. There was further activity in Alaska, but it was not part of Project Plowshare. It came somewhat later and is described in section VI C of this chapter.

VI. Related Projects and Events

In chapter 9, we had occasion to report the exhortations of Dr. William E. Lotz, who was responsible for management of much of the inhalation toxicology work in the Division of Biology and Medicine at AEC Headquarters, to the internal emitter workers to apply their energies to certain practical problems

that were requiring urgent attention. These problems had peculiar code names, not all acronyms, like Kiwi, ROVER, NERVA, and SNAP. They could hardly be regarded as Plowshare events *per se* since some had military overtones, but they resembled those we have been reviewing and belong in this discussion of "special events."

It was anticipated that the primary hazards from these would be inhalation. Hence, they were urged on at a symposium on inhalation toxicology. It has turned out that the problems were not exclusively inhalation, and what detail we can present is appropriate here rather than in chapter 9. The devices included the Nuclear Engine for Rocket Vehicle Application (NERVA); the experimental reactor for rocket propulsion that was code-named "Kiwi" after the flightless New Zealand bird, since there was no plan whatsoever that the device would leave the stationary pad; nuclear rocket propulsion, in general, "ROVER"; and, finally, the large project using radioisotopes for generation of heat that could be converted into electricity. The latter devices were used on space probes and in remote areas of the earth under the acronym "SNAP" (for Systems for Nuclear Auxiliary Power). As discussed earlier, this was the only project of those named that was technically highly successful. The others seem, in retrospect, like over-enthusiastic plans for use of nuclear energy and not always well planned. Nevertheless, they consumed several millions of dollars and required much work from the biomedical community.

A retrospective view of these enterprises and present developments was given by Broad (1982) in a general discussion of nuclear power in space, which included a second generation of SNAP, the Radioisotope Thermoelectric Generator (RTG).^(a)

A. Nuclear Rockets

The possibility of developing nuclear propelled rockets was a joint project of AEC and the National Aeronautics and Space Administration. Los Alamos played a key role in developing the technology.

The reactor designed to someday power a nuclear rocket was static tested under immobile conditions, and hence flightless like its New Zealand namesake, in a remote area of NTS. There was the usual cooperation from PHS and the Weather Bureau in Las Vegas. The tests began during early summer of 1959 and continued for a considerable period. A vigorous radiological safety program was conducted along with the engineering development.

A report on Kiwi, complete enough for our purposes, was presented by Langham (1962). He reviews the results of three tests of prototype reactors. Studies were made of the neutron and gamma-ray source strengths during operation and of fission product releases. The reactors would deliver lethal doses of neutron and gamma radiation in less than 0.1 sec at a distance of twenty feet during full operation. Thus, no one was expected to be close to these devices during the tests. At ten miles, the dose was essentially zero. Even at two miles it was only about 0.3 rad.

(a) Broad refers to SNAP as "Space Nuclear Auxiliary Power" and states that it began in 1955 and included solid-core fission reactors for the production of electricity in space. It is this author's impression that the major effort in SNAP involved only radioisotope heat sources rather than reactors.

The radiation doses from accumulated fission products attracted the most attention. The Los Alamos biomedical study (Langham 1962) presents total doses as a function of distance due to cloud passage after a maximum credible accident at the end of full-scale operation on the pad. These were 2.9 rad at one mile, 1.3 rad at three miles, and 140 mrad at ten miles, but were extremely high close in. He also presents anticipated dose rates as a function of time after impact if a 1,000-MW reactor should land intact or be destroyed and the fission products spread uniformly over either 0.1 or 1.0 mi², or land in shallow water, or enter the atmosphere from orbit. Various times of operation were incorporated into the estimates. Finally, he compares the contribution of fission products from projected nuclear rocket operations to then-extant tropospheric and stratospheric fallout. There was no doubt from all of this that evaluation of the initial dose rate was essential to management of any incidents, since the time of operation, time after shutdown, etc., could make enormous differences.

More actual data on fission-product production and fallout were contained in an oral presentation by Isaac Van der Hoven of the U.S. Weather Bureau in Las Vegas at the 187th National Meeting of the American Meteorological Society at Eugene, Oregon (Van der Hoven 1960). The presentation concerned mostly a fallout model but also contained the data. Among other things, Van der Hoven showed that the distribution of radioactivity was not uniform among particle sizes. The 5- to 20- μ range contained about 39% of the beta and 38% of the gamma activity, and the particles above 44 μ contained 34% and 38%, respectively.^(a) The closest third was the range 20 μ to 44 μ . Particles below 5 μ carried much less of the activity. The decay rates of these fission products were as $t^{-1.39}$ from H + 50 to H + 145 hr, and as $t^{-1.04}$ from H + 145 to H + 280 hr. The total integrated fallout from the Kiwi-A test, to which all of this refers, was 0.011 MCi. For comparison, a typical detonation in the Hardtack Phase II series (Otero) under way at the time, produced about 0.55 MCi of fission products.

The general conclusions from this work were that the release of fission products can be far from minuscule and is something to be reckoned with. Both site of firing and the trajectory would have to be carefully chosen. It does appear that a significant fraction of the fission products from the prototype device might be above respirable size. Thus, inhalation hazards would not be of exclusive concern.

The fuel elements of the experimental reactor for ROVER contained about 10^{12} particles of uranium-235 carbide ($^{235}\text{UC}_2$) of about 100- to 200- μm diameter (Dean and Langham 1969). The particles would have undergone as many as 10^{13} fissions and have dose rates of 10^8 rad per hour at thirty minutes after reactor shutdown. Even one of these on the skin could be of concern.^(b) Thus, the hazard analysis needed consideration of the effects in both lung and skin of some very hot particles.

The paper by Dean and Langham is an excellent discussion of the possible tumorigenicity of various sizes and activities of particles. It included some experimental work with three monkeys and two men. The calculated results are shown in table 14.2. The conclusion was that five hundred biological sites would have to be exposed to the highest dose to be certain of producing a tumor.

(a) Remember the 44- μ rule developed by UCLA for NTS weapons fallout?

(b) Such particles could also be of significance in the upper respiratory tract according to work of Sanders at PNL.

TABLE 14.2. Exposure of Human Skin to Fissioned $^{235}\text{UC}_2$ Microspheres

Fissioned $^{235}\text{UC}_2$ Sphere	Dia. (μ)	Exposure Time (hr)	Dose at Basal Layer (rad)	Tumor Probability
1	174	1.6	14,200	8.1×10^{-4}
2	159	5.3	40,000	8.1×10^{-3}
3	140	6.1	54,000	2.0×10^{-3}

Source: Modified from Dean and Langham 1969. Note: Calculations based on model developed in the cited paper and the noted effects of the actual skin exposures. Reprinted with permission of Pergamon Press, Elmsford, New York, copyright 1969.

Again, it is difficult to say that biomedical problems led the way to the demise of this project. Clearly they were not negligible. This author remembers being present at a meeting where it was stated firmly that a nuclear rocket for propulsion of a space vehicle could never be used in the launch phase or in earth's lower atmosphere. That would have to be done with conventional chemical propellants with the nuclear rocket taking over to help move the vehicle into higher orbits or into the solar system or beyond. Even though the project seems dead for now, the presence of these biomedical evaluations may be of use should it be resurrected or other problems arise with similar characteristics.

B. SNAP

As indicated earlier, SNAP is the only program of this group that went through development and became operational. Today there are many thermoelectric generators on satellites now in orbit or in space trajectories, on the moon, and in remote areas of the world, all obtaining the heat for their electrical power from the presence of large quantities of radioisotopes. A summary of the SNAP devices launched through the mid-1970s is given in table 14.3.

Note that these devices contain primarily ^{238}Pu with small (relatively) quantities of ^{239}Pu . Almost a million curies of ^{238}Pu have been incorporated in these devices. The first such source contained ^{210}Po and was demonstrated personally by President Eisenhower by having it light a small electric bulb on his desk. Later, ^{90}Sr was used, but the alpha emitters have the advantage of requiring less shielding. Lotz (1964) lists eighteen materials used or proposed for SNAP devices. However, the choices gradually narrowed down, and plutonium became, and is, the most common material used. There is no question but the very considerable increase in demand for ^{238}Pu resulting from this choice led to much of the experimental work with this isotope that we have already reviewed.

There were two major safety concerns with these devices: mishaps during the early phases of launch, which would bring the device violently back to earth; and uncontrolled orbital decay and atmospheric re-entry. The engineers took care of the first problem by exceedingly sturdy construction that withstood the most severe tests without breaching the source container. By contrast, it was determined, for the early generation of devices, that controlled re-entry from orbit could not be guaranteed and that the design should assure complete burn up of the fuel core in the upper atmosphere.

TABLE 14.3. Summary of Launched Space Nuclear Power Systems

Mission	Launch Date	Fuel Form	Activity, Ci		Disposition
			²³⁸ Pu	²³⁹ Pu	
Transit 4-A	6/61	Plutonium metal	1,800	1.3	In >1000-yr earth orbit
Transit 4-B	11/61	Plutonium metal	1,800	1.3	In >1000-yr earth orbit
Transit 5-BN-1	9/63	Plutonium metal	17,000	13	In >1000-yr earth orbit
Transit 5-BN-2	12/63	Plutonium metal	17,000	13	In > 1000-yr earth orbit
Transit 5-BN-3	4/64	Plutonium metal	17,000	13	Aborted, burned up on reentry
Nimbus B-1	5/68	PuO ₂ microspheres	34,400	25	Aborted, containers recovered
Nimbus 111	4/69	PuO ₂ microspheres	37,600	28	In ~3000-yr earth orbit
Apollo 12	11/69	PuO ₂ microspheres	44,500	33	On lunar surface
Apollo 13	4/70	PuO ₂ microspheres	44,500	33	Aborted, intact in Pacific Ocean
Apollo 14	1/71	PuO ₂ microspheres	44,500	33	On lunar surface
Apollo 15	7/71	PuO ₂ microspheres	44,500	33	On lunar surface
Apollo 16	1/72	PuO ₂ microspheres	44,500	33	On lunar surface
Pioneer F	3/72	Plutonium molybdenum cermet	80,000	59.5	Ejected from solar system
Transit	9/72	Plutonium molybdenum cermet	24,000	18	In <1000-yr earth orbit
Apollo 17	12/72	PuO ₂ microspheres	44,500	33	On lunar surface
Pioneer G	4/73	Plutonium molybdenum cermet	80,000	59.5	Ejected from solar system
Viking-1	8/75	Plutonium molybdenum cermet	42,000	31	On Mars surface
Viking-2	9/75	Plutonium molybdenum cermet	42,000	31	On Mars surface
Les 8/9	3/76	Pressed PuO ₂	280,000	208.4	In >100,000-yr earth orbit
Total			941,600	700	

Source: Reset from Dobry 1980.

In later generation devices, the engineering was able to meet an intact re-entry as well as intact impact philosophy (Dobry 1980).

These devices were not put into orbit overnight. There was a SNAP Hazards Safety Committee of the AEC, which met often and weighed the alternatives diligently. Health hazards played an important role. Many meetings were held

under the aegis of the Division of Biology and Medicine (DBM). The results of two of these were kindly made available by Dr. H. D. Bruner, who had much of the responsibility in Headquarters.^(a) The members were, in addition to Dr. Bruner, Roy Albert (New York University); William Bair (PNL); Birney Fish (ORNL); Wright Langham (Los Alamos Scientific Laboratory [LASL]); Thomas Mercer (Rochester); Roger McClellan (Lovelace); Arthur Tamplin (LLL); and William Lotz (DBM/AEC). It was soon decided that gastrointestinal absorption was so low and that the protection afforded by the cornified epidermal layers in the skin was sufficient to eliminate surface deposition and ingestion as important health problems from this alpha emitter. Inhalation and effects on lung were considered the major concern, although thought was given to gonads to the extent of careful calculations of how much the maximum possible amount from SNAP devices might add to the plutonium already accumulated from weapons-testing fallout. It was considered not sufficient to make much difference biologically.

Obviously, particle size was an important parameter in estimating the inhalation hazard from a reentry burn up of a SNAP device. Many of the ideas that later triggered the hot particle issue came up for full discussion at the meetings of the committee. It was agreed that full burn up would probably result in a predominance of very small particles (i.e., it would be a fume). Thus, hot particles would not be present initially. However, they might form later, either by coalescence in the atmosphere or in the lung. There was also consideration of the size of the populations potentially exposed and of what guidance should be given to agencies concerned in the event of a mishap.

An opportunity to test the calculations came unexpectedly. On April 21, 1964, a navigational satellite carrying a SNAP Device (SNAP 90A, indicated in table 14.3 as "Transit 5-BN-3") containing 17 kCi of ^{238}Pu (about 1 kg) failed to reach full orbital flight. The payload re-entered the atmosphere in the Southern Hemisphere and burned completely (Krey 1967).^(b) Long-term balloon and aircraft sampling and integrated fallout figures determined from samples of soil collected from sixty sites worldwide are told in detail by Hardy, Krey, and Volchok (1972). About 13 kCi could be accounted for, most of it in very small particle sizes that could remain aloft for years (half-residence time, fourteen months). The distribution, while localized in the Southern Hemisphere to begin with, gradually became worldwide, although it never became uniform. Because of the enormous dilution, no inhalation or other health hazards could be identified. Nevertheless, we must remember that none of the larger particles could have still been aloft by the time the sampling program got under way. We must assume that either there were very few of these, or that they fell in areas where they would not be detected (which at the time of the abort was nearly everywhere around the area involved).

The health hazards associated with SNAP devices were probably more thoroughly researched than any nuclear energy undertaking of the day, in proportion to their importance. So far, it appears that the planning and performance have been adequate. Even the one abort seems to have added only to the inventory of plutonium, not to discernible health effects.

(a) He is now at Bonita Springs, Florida. Dr. Bruner's reminiscences on a taped interview were also extremely helpful in this and other areas.

(b) There were two other aborts (see table 14.3). However, the containers remained intact in these instances.

C. More Alaskan Operations^(a)

In chapter 12 on fallout, and elsewhere, we referred to the special food-chain problems in arctic regions that involved vectors such as lichen-reindeer or caribou (or other edible vector)-Eskimo. A fairly large ecological investigation was mounted. Much of it was reported in the third symposium on radioecology, (see, for example, Hanson and Eberhardt 1971; Holleman et al. 1971; Koranda and Martin 1971; Martin and Koranda 1971; and many others). There was similar work in northern Europe, particularly by J. Miettinen of the University of Helsinki, Finland. Some of this was carried out in the interior of Alaska, and some on the coast at Amchitka Island in the far reaches of the Aleutians. Three nuclear tests were conducted on Amchitka Island. The first, "Long Shot" was a low-yield nuclear test conducted on October 29, 1965, for seismic calibration purposes. A few biological observations were conducted relative to this nuclear test by the University of Washington. As told in a personal interview with Allyn Seymour of the University of Washington (1979), one set of observations conducted with the "Long-Shot" test concerned fish eggs that were undergoing embryological development in a stream close enough to the shot to be subjected to considerable jarring and shaking. Some of the capsules were disturbed and moved a short distance downstream. However, the survival was on the order of 90%. Also, samples of fish and plants were brought back to the laboratory for radiological analysis. This was primarily for monitoring purposes to check on possible releases of activity in these unstable rock formations. None were found.

There was little work relative to radionuclides in biological materials in this operation.

The other two nuclear tests, "Milrow" (October 2, 1969) and "Cannikin" (November 6, 1971), were of much higher yield than any underground detonations previously conducted by the United States (Milrow, approximately 1 MT, and Cannikin, approximately 5 MT). These weapons-related tests were conducted on Amchitka because no suitable locations could be found in the conterminous forty-eight states.

An extensive program was conducted to predict and determine the effects of these tests on the bioenvironment. This program was initiated in 1967 by Battelle Memorial Institute (BMI). In 1969, a comprehensive review was conducted of the bioenvironmental questions that should be addressed, and a comprehensive Amchitka Bioenvironmental Program was developed and administered by the NVO of AEC. Principal persons in developing the plans for this program were Jared Davis of NVO, Richard Davidson of BMI, and Melvin Merritt of Sandia Laboratories, Albuquerque, New Mexico, with the assistance of technical experts in various specific fields such as sea otter ecology and North Pacific oceanography. The studies included geology, anthropology, oceanography, marine biology, marine mammals, and radioecology. The principal institutions that participated in the research were BCL; U.S. Geological Survey, Denver and Lakewood, Colorado; Air Resources Laboratory, NOAA, Las Vegas, Nevada; Sandia Laboratories, Albuquerque, New Mexico; Ohio State University, Brigham Young University, Provo, Utah; NVO; University of Arkansas, Fayetteville, Arkansas; Utah State University, Logan, Utah; Northwest Fisheries Center, NOAA, Auke

(a) The author is indebted to Dr. Jared Davis for information and assistance in preparing this section.

Bay, Alaska; University of Washington, Seattle, Washington; U.S. Fish and Wildlife Service, Anchorage, Alaska; and University of Arizona, Tucson, Arizona.

The plans and results were gathered in a volume comparable to the one on Cape Thompson, cited earlier. It was edited by Merritt (Sandia) and Fuller (BCL) and entitled, *The Environment of Amchitka Island, Alaska* (Merritt and Fuller 1977). Besides the discussions directly relevant to the tests, it contains reviews of the long history of the Aleutians, the slaughter of sea otters to near extinction, the ill-advised importation of blue foxes, the effects of World-War-II operations on the delicate ecology of this area, and much else. Only one chapter addresses radionuclides in air, water, and the biota (Seymour and Nelson 1977). Natural and fallout radionuclides and items of special interest such as tritium, radioiron, and radiostrontium were included.

Samples were collected principally from areas considered likely to be contaminated by seepage of radionuclides from the underground detonation sites. The eighty-one types of organisms collected included mammals, fish, birds, invertebrates, marine algae, freshwater and land plants, with total samples numbering several thousand. The most abundant radionuclides in the samples were the naturally occurring ^{40}K and ^7Be , with the most significant manmade nuclide being ^{137}Cs from worldwide and northern latitude fallout. There was no indication of escape of radionuclides from either of the three underground detonations.

The above does not mean that Amchitka suffered no effects from these heavy detonations. There were numerous rock slides, some of which buried living organisms, a section of the so-called bench along the ocean near Shot Cannikin was permanently uplifted to the extent that the littoral area became dry and its populations lost. Two or three lakes were wholly or partially drained. These effects are summarized by Fuller and Kirkwood (1977). However, none of them involved any release of radionuclides or contamination of the environment.

In retrospect, the effects of the earlier activities of man on Amchitka, e.g., World-War-II construction, roads, etc., were more visible and permanent than those of the three nuclear tests. Naturally, it would have been a different story if the detonations had been aboveground instead of several thousand feet below ground.

D. Mississippi Test

There was much interest in the results of a nuclear detonation in a typical salt dome. After much searching, an ideal geological structure was pinpointed near Hattiesburg, Mississippi, at a small town called Baxterville. A small detonation, less than 5 kt, took place in this salt dome (Carter 1979).^(a) The primary biomedical activity was surveillance carried out by the PHS. Primary interest here, too, was in seismic phenomena. There was no release of radioactivity from these shots. The primary reason for describing them here is to illustrate the ubiquitousness of the surveillance activities of the PHS.

(a) This was not included in the list of announced U.S. tests.

VII. Summary and Commentary

There were several projects centered on actual or potential environmental contamination with radioactive materials that were quite different from either the nuclear weapons tests described in chapter 12 or the experimental work described in chapter 13. Most of these have been brought together in this chapter. Although termed "tests," they involved much field and laboratory research. However, they were not rigidly controlled scientific experiments, and for present purposes we thus call them "special tests."

Some of the earliest of these revolved around the potential for environmental contamination with plutonium and other weapons constituents in the event of a nonnuclear detonation (i.e., the high explosive only) of such a device. There were organized tests at the Nevada Test Site in 1956 and 1957 (Project 56 and Test Group 57 of Operation Plumbbob) and a joint U.S.-U.K. operation at the Tonopah Test Range in Nevada (Operation Roller Coaster). These tests were supplemented by two unplanned incidents involving nuclear weapons—one at Palomares, Spain, the other at Thule, Greenland.

Project 56 had no biomedical components. It was aimed at measurement of physicochemical behavior of released airborne plutonium. Test Group 57 generated extensive biomedical data from animals exposed at the time of the one-point detonation and also after chronic exposure for up to 160 days in the contaminated environment. No long-term or short-term effects of the released plutonium could be found, but the period of observation was short. A major conclusion of the experiment was that the potential radiation dose to major organs from cloud passage was of greater importance than that from extended sojourns in a plutonium-contaminated environment. This was the exact opposite of expectations. Also, it appeared that the plutonium content of the air fell rather rapidly with time, also not expected. There were, however, many puzzling inconsistencies in the data and disappointments in the amount learned from the long-term air-sampling program.

Operation Roller Coaster, characterized as the largest inhalation experiment ever undertaken under field conditions, provided good characterization of the aerosols formed and more reliable deposition and clearance kinetics data for lung and other tissues. It seemed to confirm the probably greater importance of cloud passage over later chronic exposure. However, Operation Roller Coaster did not have an extensive chronic phase and, because of the cost and time involved in plutonium radiochemistry, there is still some work to be done.

All of the information from these so-called "safety tests" was used by the military to design configurations for storage and handling of nuclear weapons and for establishment of allowable ground contamination levels of plutonium in case of an incident.

Much effort was expended in the years after these safety tests to evaluate the retention and movement of plutonium in soils and biota in and around these and other sites. This was done largely under the aegis of a managing organization known as the Nevada Applied Ecology Group. This work, too, is still under way, although now reduced considerably in volume. The chapter provides an overview of the principal findings.

Not all of the special tests concerned plutonium or the transplutonic elements. In a little known series of tests at the Idaho Falls site, there were special tests of fission product releases. The *raison d'être* was the now-defunct "Aircraft Nuclear Propulsion Project." It was anticipated that fission products released from a reactor under the conditions of nuclear propulsion might be in quite

different form and behave differently from the fission products in fallout. Elaborate aerosol sampling and measurement facilities were provided, and excellent provisions were made for exposing, caring for, and measuring the radioactivity in animals exposed to releases of fission products. The source was purposely burned reactor fuel elements. The results provided much confirmation of the laboratory work described in chapter 9 but also some differences. The length of time the fuel element had been in the reactor, and the time since its removal, made a large difference in the composition of the released fission products. There were comparable differences in their behavior in the biological systems. This effort was known as "FPFRT" for Fission Product Field Release Tests.

The chapter describes several aspects of Project Plowshare, an extensive and ambitious part of the Atoms for Peace Program. The prime idea was the use of nuclear explosives for giant earth-moving or digging projects. There were extensive computations of possible contamination of the environment and thus the feasibility of digging a new canal between the Atlantic and Pacific Oceans over a route that would avoid costly locks and could be wider and deeper than the present Panama Canal. It appears likely that concern over the lingering contamination did much to cancel this canal project. The pertinent findings are described.

Other aspects of Project Plowshare were several crater-digging experiments at the Nevada Test Site and, most interesting and rewarding, stimulation of the flow of natural gas entrapped underground in impermeable strata by fracturing them with nuclear explosives. The three tests were U.S. government-industry cooperative ventures. They were named "Project Gasbuggy," "Project Rulison," and "Project Rio Blanco." The first was conducted in New Mexico; the other two in Colorado. There is no doubt that the fracturing of the entrapped strata, brought about by nuclear explosion, released appreciable quantities of natural gas. One reliable investigator stated that the process could double the amounts of natural gas available in the United States. The principal radioactive contaminant of the gas was tritium, a radionuclide on the low end of the hazard scale (chapter 10), but not inconsequential. The gas was never used commercially, nor was the process carried beyond the three tests. The idea of piping gas containing even a small increase of radioactivity due to the operations of man into homes and factories was simply not acceptable.

Another category of special environmental test projects concerned the nuclear rocket "Kiwi," which was static-tested at the Nevada Test Site, and an experimental reactor called "ROVER." In these instances, it was demonstrated that possible contamination of the skin with radioactive particles of ^{235}U carbide might constitute the prime health concern. While considered significant, these potential hazards were perhaps less the cause of the project's termination than in some other cases, but the record is murky in this regard.

A large number of conferences, much calculation, and some measurements, were part of the biomedical aspects of "SNAP" (System for Nuclear Auxiliary Power). This project concerned the use of radioisotopes as heat sources for the thermoelectric generation of electric power. The early models used ^{210}Po , but most of the later models used kilocuries of ^{238}Pu .

The program has perhaps been the most successful facet of Project Plowshare. Many space flights have received and are receiving power for vital scientific observations from SNAP units. SNAP power took part in the moon mission (Apollo 17), and units are now in place and powering experiments on the moon. Two Mars landers use SNAP power. In addition, many such units are operating in isolated areas of the earth.

Almost a million curies of ^{238}Pu have been manufactured and placed in these devices. The planning for safety has paid off. The two missions that aborted with these devices aboard ended by burning up in the upper atmosphere with deposit of 17,000 Ci of ^{238}Pu in the stratosphere in one case and recovery of the containers intact in the other. The stratospheric contamination from the first case has exchanged slowly with the troposphere but can still be measured as an entity. It is not considered of biomedical significance.

Other special environmental tests concerned the Alaskan environment and exploration of the effects of a nuclear explosion in an underground salt dome in Mississippi. Not much can be said about biomedical results from these.

These special tests were very costly in money and manpower. There were many who felt that the same expenditure on basic research would have brought greater rewards. It is doubtful, however, if the sources of funds for these operations could have transferred them to other research undertakings. All were bound to specific engineering and safety enterprises. Naturally, the results are harder to get and harder to judge than comparable laboratory efforts. The degree of randomness is obviously greater. Yet, there are those who insist that there is no substitute for tests under field-operating conditions and that they are quite justified. The chronology of results in this chapter should help answer that question.

Note 1—List of Roller Coaster Reports

A. Reports Bearing POR-WT Numbers

Project 2.1 - Soil Deposition

William S. Johnson, Sr.: Project Officer, Eberline Instrument Corporation, Santa Fe, NM: POR-2501 (ST-2501) January 31, 1966, "Official Use Only" (OUO)

Project 2.2 - Air Sampling Measurements

Joseph C. Maloney: Project Officer, U.S. Army Nuclear Defense Laboratory, Edgewood Arsenal, MD, (with participants from General Dynamics, Ft. Worth, TX): POR-2502 (WT-2502) October 21, 1965 (OUO)

Project 2.3 - Fallout Collection

P.W. Krey, Project Officer, R.E. Fried and R.J. Schultz, Isotopes, Inc., Westwood, NJ: POR-2503 (WT-2503) August 23, 1965 (OUO)

Project 2.4 - Micro-Meteorological Measurements (U)

R.W. Titus: Project Officer, U.S. Weather Bureau Research Station, Las Vegas, NV: POR-2504 (WT-2504) July 6, 1965

Project 2.5 - Alpha Survey

W.S. Johnson, Sr.: Project Officer, Eberline Instrument Corporation, Santa Fe, NM: POR-2505 (WT-2505) January 31, 1966

Project 2.6a - Special Particulate Characterization

R.K. Fuller: Project Officer, U.S. Naval Radiological Defense Laboratory, San Francisco, CA: POR-2506 (WT-2506) November 16, 1965 (OUO)

Project 2.6b - Special Particulate Analyses

R.D. Sherwood: Project Officer, Isotopes, Inc., Westwood, NJ: POR-2507 (WT-2507) May 26, 1966 (OUO)

Project 2.6c - Special Particulate Characteristics

C.D. Dunn: Project Officer, Tracer Laboratories Richmond, CA: POR-2508 (WT-2508) September 17, 1965 (OUO)

Project 2.6d - Special Particulate Analyses (Soil)

J.K. Perry: Project Director, Colorado School of Mines Research Foundation, Golden, CO: POR-2509 (WT-2509) May 26, 1966 (OUO)

Project 2.7 - Balloon Support

H.G. Laursen: Project Officer, Sandia Corporation, Albuquerque, NM: POR-2510 (WT-2510) May 21, 1965 (OUO)

Project 2.8 - Off-Site Survey

J.S. Coogan: Project Officer, Southwestern Radiological Health Laboratory, Las Vegas, NV: POR-2511 (WT-2511) September 17, 1968

Project 4.1 - Plutonium Uptake by Animals

R.H. Wilson: Project Officer, University of Rochester, Atomic Energy Project, Rochester, NY

Project 5.1a - Sample Processing Facility

A.L. Baietti: Project Officer, Tracer Laboratory, Richmond, CA: POR-2513 (WT-2513) July 30, 1965

Project 5.1b - Sticky Wire Evaluation

A.L. Baietti: Project Officer, Tracer Laboratory, Richmond, CA: POR-2514 (WT-2514) May 23, 1966

Project 5.2/5.3a - Radiochemical Analysis of Biological and Physical Samples

H.E. Menker: Project Officer, Hazleton-Nuclear Science Corporation, Palo Alto, CA: POR-2515 (WT-2515) May 24, 1966 (OUO)

Project 5.2/5.3c - Radiochemistry

E.L. Geiger: Project Officer, Eberline Instrument Corporation, Santa Fe, NM: POR-2517 (WT-2517) September 17, 1965 (OUO)

Project 5.2/5.3d - Laboratory Analyses of Roller Coaster Samples

P.W. Krey: Project Officer, Isotopes Incorporated, Westwood, NJ: POR-2518 (WT-2518) August 20, 1965 (OUO)

Project 9.5 - Technical Photography

R.P. Beasley: Project Officer, Sandia Corporation, Albuquerque, NM: POR-2519 (WT-2519)

B. University of Rochester Atomic Energy Project Reports

Report UR-665

See References for this chapter

C. U.K. Reports

AWRE Report No. 0-29/65 - *A Preliminary Evaluation of the Biological Measurements on Operation Roller Coaster*

K. Stewart, J.L. Terry, D.M.C. Thomas, and R.H. Wilson

AWRE Report No. 076/67 - *Final Evaluation of the Biological Measurements on Operation Roller Coaster (Joint U.S./U.K. field experiment)*

K. Stewart and R. H. Wilson

D. Published Document

See Wilson and Terry 1965a in the References for this chapter

Note 2—Some Reports from the Nevada Applied Ecology Group

Nevada Operations Office, DOE (ERDA, AEC), Las Vegas, NV

Note: Each report contains a series of papers on various aspects of the program. They range from simple progress reports to detailed and sophisticated presentations of

experimental data. There were also many publications in the open literature. Many of these are cited in the ORNL-EIS reports and NVO-192.

ORNL-EIS-72-21 *Environmental Aspects of Plutonium: A Selected Annotated Bibliography*. September 1972. Supplements in 1973, 1974, 1975, 1976, and 1977

NVO-142 *The Dynamics of Plutonium in Desert Environments - AEC Progress Report*. July 1974, USAEC, Nevada Operations Office, eds: P.B. Dunaway and M.G. White

NVO-153 *The Radioecology of Plutonium and Other Transuranics in Desert Environments*. June 1975, NAEG Program Report, USERDA, eds: M.G. White and P.B. Dunaway

NVO-159 *Studies of Environmental Plutonium and Other Transuranics in Desert Ecosystems*. NAEG Progress Report, USERDA, eds: M.G. White and P.B. Dunaway

NVO-167 *Ecology of the Nevada Test Site: A Narrative Summary and Annotated Bibliography*. T. P. O'Farrell and L. A. Emery: Applied Ecology and Physical Center-Desert Research Institute, University of Nevada System, Boulder City, NV; May 1976

NVO-166 *Nevada Applied Ecology Group - Procedures Handbook for Environmental Transuranics*: 2 Volumes. October 1976, USERDA, eds: M.G. White and P.B. Dunaway

NVO-171 *Environmental Plutonium on the Nevada Test Site and Environs*. June 1977, USERDA, eds: M.G. White, P.B. Dunaway, and W.A. Howard

NVO-178 *Transuranics in Natural Environments - A Symposium at Gatlinburg, TN*. October 1976, NAEG, June 1977, USERDA, Eds: M.G. White and P.B. Dunaway

NVO-181 *Transuranics in Desert Ecosystems*. NAEG November 1977, USDOE, eds: M.G. White, P.B. Dunaway, and D.L. Wireman

NVO-192 *Selected Environmental Plutonium Research Reports of the NAEG*. June 1978, 2 Volumes, eds: M. G. White and P. B. Dunaway

ORNL-EIS-127 (NVO/AEIC-7811) *Nevada Applied Ecology Group Publications*. Nevada Applied Ecology Information Center, July 1978, eds: M. G. White and H. H. Pfuderer.

NVO-272 *The Dynamics of Transuranics and other Radionuclides in Natural Environments*. December 1985 (published September 1987), eds. W. A. Howard and M. G. Fuller

References

- Aarkrog, A. 1971. Radioecological investigations of plutonium in an arctic marine environment. *Health Phys.* 20:31-47.
- Aarkrog, A. 1972. Reexamination of plutonium at Thule, Greenland, in 1970. In *Proceedings of a symposium on radioecology applied to the protection of man and his environment*, EUR-4800, pp. 1213-19. Held in Rome, September 7-10, 1971. European Atomic Energy Community.
- Aarkrog, A. 1977. Environmental behaviour of plutonium accidentally released at Thule, Greenland. *Health Phys.* 32:271-84.
- Aircraft Nuclear Propulsion. 1959. *Fission products field release test-I*. Nuclear Aircraft Research Facility, Convair-Fort Worth. ANP document no. NARF-59-32T F2K-9-140, Report AFSWC TR-59-44. Albuquerque, N. Mex.: Air Force Special Weapons Center.
- Aircraft Nuclear Propulsion. 1960. *Fission products field release test II*. Nuclear Aircraft Research Facility, Convair-Fort Worth. ANP document no. NARF-60-10T, F2K-9-149, Report AFSWC TR-60-26. Albuquerque, N. Mex.: Air Force Special Weapons Center.
- ANP. See Aircraft Nuclear Propulsion.

- Anspaugh, L. R., J. J. Koranda, and W. L. Robison. 1971. Environmental aspects of natural gas stimulation experiments with nuclear devices. In *Radionuclides in ecosystems*, ed. D. J. Nelson, CONF-710501-P1, pp. 37-52. Proceedings of the 3d national symposium on radioecology held in Oak Ridge, Tenn., May 10-12, 1971. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Au, F. H. F. and W. F. Beckert. 1978. Microbiological contribution to plutonium bio-availability and transport in the environment. In *Selected environmental plutonium research reports of the NAEC*, NVO-192, pp. 95-108. Las Vegas: U.S. Department of Energy.
- Beckert, W. F. and F. H. F. Au. 1976. Plutonium uptake by a soil fungus and transport to its spores. In *Transuranium nuclides in the environment*, pp. 337-45. Proceedings of a symposium held in San Francisco, November 17-21, 1975. Vienna: International Atomic Energy Agency.
- Bloom, S. G. and W. E. Martin. 1978. The effect of variations in source term and parameter values on estimates of radiation dose to man. In *Selected environmental plutonium research reports of the NAEC*, NVO-192, vol. 2, pp. 513-36. Las Vegas: U.S. Department of Energy.
- Broad, W. J. 1982. Nuclear power for militarization of space. *Science* 218:1199-1201.
- Bunch, D. F., ed. 1966. *Controlled environmental radioiodine tests progress report number two*. IDO-12053. Springfield, Va.: National Technical Information Service.
- Carter, M. W. 1971. Environmental Protection Agency, Southwestern Radiological Health Laboratory, Las Vegas. Rulison open file. [Cited by Anspaugh et al. 1971.]
- Carter, M. W. 1979. Taped interview at Georgia Institute of Technology, April 10, 1979.
- Carter, M. W. and O. R. Placak. 1956. Plutonium contamination found offsite following one-point detonations. In *The shorter-term biological hazards of a fallout field*, eds. G. M. Dunning and J. A. Hilcken, pp. 185-87. Proceedings of a symposium held December 12-14, 1956. Washington, D.C.: Atomic Energy Commission.
- Chertok, R. J. and S. Lake. 1971a. Availability in the peccary pig of radionuclides in nuclear debris from the Plowshare Excavation Buggy. *Health Phys.* 20:313-16.
- Chertok, R. J. and S. Lake. 1971b. Biological availability of radionuclides produced by the Plowshare Event Schooner—I. Body distribution in domestic pigs exposed in the field. *Health Phys.* 20:317-24. [See also R. J. Chertok and S. Lake. 1971. Retention and excretion by pigs of radionuclides produced by the Plowshare Event Schooner. In *Health physics aspects of nuclear facility siting*, eds. P. G. Voillequé and B. R. Baldwin, vol. 2, pp. 475-76. Proceedings of the 5th annual Health Physics Society midyear topical symposium held in Idaho Falls, November 3-6, 1970.]
- Cowser, K. E., S. V. Kaye, P. S. Rohwer, W. S. Snyder and E. G. Struxness. 1967. *Dose-estimation studies related to proposed construction of an Atlantic-Pacific Inter-oceanic Canal with nuclear explosives: Phase I*. AEC report ORNL-4101. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Dean, P. N. and W. H. Langham. 1969. Tumorigenicity of small highly radioactive particles. *Health Phys.* 16:79-84.
- Dobry, T. J., Jr. 1980. Transuranic elements in space nuclear power systems. In *Transuranic elements in the environment*, ed. W. C. Hanson, DOE/TIC-22800 pp. 83-85. Springfield, Va.: National Technical Information Center.
- Essington, E. H. 1978. Soil radioactivity-distribution studies for the Nevada Applied Ecology Group. In *Selected environmental plutonium research reports of the NAEC*, NVO-192, pp. 177-243 [see especially p. 180]. Las Vegas: U.S. Department of Energy.
- Essington, E. H., H. Nishita, and D. J. Steen. Undated. *The recent movement of radionuclides in soils contaminated with fall-out materials from underground thermal nuclear detonation*. Project Sedan report PNE-239 F (UCLA).
- Essington, E. H., E. B. Fowler, R. O. Gilbert, and L. L. Eberhardt. 1976. Plutonium, americium and uranium concentrations in Nevada Test Site soil profiles. In *Transuranium nuclides in the environment*, pp. 157-72. Proceedings of a symposium held in San Francisco, November 17-21, 1975. Vienna: International Atomic Energy Agency. [Also released as LA-UR-75-1770. Note: work done at Los Alamos Scientific Laboratory, Los Alamos, N. Mex. and Battelle, Pacific Northwest Laboratories, Richland, Wash.]

- Fountain, E. L. 1963. Iodine uptake from a single inhaled exposure—An abstract. *Health Phys.* 9:1215.
- Fuller, R. G. and J. B. Kirkwood. 1977. Ecological consequences of nuclear testing. In *The environment of Amchitka Island, Alaska*, eds. M. L. Merritt and R. G. Fuller, TID-26712, chapter 26, pp. 627-49. Springfield, Va.: National Technical Information Center.
- Gerber, C. R., R. Hamburger, and E. W. S. Hull. 1967. Plowshare. Part of series entitled *Understanding the atom*. Oak Ridge, Tenn.: U.S. Atomic Energy Commission, Division of Technical Information.
- Gilbert, R. O., L. L. Eberhardt, E. B. Fowler, E. H. Essington, and E. M. Romney. 1976. Statistical analysis and design of environmental studies for plutonium and other transuranics at NAEG "safety-shot" sites. In *Transuranium nuclides in the environment*, pp. 449-60. Proceedings of a symposium held in San Francisco, November 17-21, 1975. [Note: Work done at Battelle, Pacific Northwest Laboratories (Gilbert and Eberhardt); Los Alamos Scientific Laboratory (Fowler and Essington); and UCLA (Romney).]
- Gotchy, R. L. 1971. *Project Rulison radioactivity, high-rate production testing*. Las Vegas: U.S. Atomic Energy Commission, Nevada Operations Office. [Cited by Anspaugh, Koranda, and Robison 1971.]
- Hanson, W. C. 1971. Fallout radionuclide distribution in lichen communities near Thule. *Arct. J. Arct. Inst. N. Am.* 24:269-76.
- Hanson, W. C. 1972. Plutonium in lichen communities of the Thule, Greenland, region during the summer of 1968. *Health Phys.* 22:39-42.
- Hanson, W. C. 1976. Studies of transuranic elements in arctic ecosystems. In *Radioecology and energy resources*, ed. C. E. Cushing, Jr., Ecological Society of America special publ. no. 1, pp. 29-39. Proceedings of the 4th national symposium on radioecology held at Oregon State Univ., May 12-14, 1975. Stroudsburg, Pa.: Dowden, Hutchinson & Ross, Inc.
- Hanson, W. C. 1980. Transuranic elements in arctic tundra ecosystems. In *Transuranic elements in the environment*, ed. W. C. Hanson, DOE/TIC-22800, pp. 441-58. Springfield, Va.: National Technical Information Center.
- Hanson, W. C. and L. L. Eberhardt. 1971. Cycling and compartmentalizing radionuclides in Northern Alaskan lichen communities. In *Radionuclides in ecosystems*, ed. D. J. Nelson, CONF-710501-P1, pp. 71-75. Proceedings of the 3d national symposium on radioecology held in Oak Ridge, Tenn., May 10-12, 1971. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Hardy, E. P., P. W. Krey, and H. L. Volchok. 1972. *Global inventory and distribution of Pu-238 from SNAP-9A*. HASL-250. New York: U.S. Atomic Energy Commission, Health and Safety Laboratory.
- Harris, P. S., E. C. Anderson, and W. H. Langham. 1956. *Contamination hazard for accidental non-critical detonations*. LA-2079. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory. [Quoted from Wilson, Thomas, and Stannard 1960.]
- Harrison, F. L. 1973. Availability to aquatic animals of short-lived radionuclides from a Plowshare cratering event. *Health Phys.* 24:331-43.
- Holleman, D. F., J. R. Luick, and R. G. White. 1971. Transfer of radiocesium in milk from reindeer cow to calf. In *Radionuclides in ecosystems*, ed. D. J. Nelson, CONF-710501-P1, pp. 76-80. Proceedings of the 3d national symposium on radioecology held in Oak Ridge, Tenn., May 10-12, 1971. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Iranzo, E. and S. Salvador. 1970. Inhalation risks to people living near a contaminated area. Paper presented at the 2d international congress of the International Radiation Protection Association, held at Brighton, England, May 3-8, 1970 (abstract no. 317). International Radiation Protection Association.
- Johnson, W. S., Sr. 1982. Letter to J. N. Stannard dated January 8, 1982. [Mr. Johnson was intimately involved in the work of Project 56. He is now president of Asset and Investment Monitoring, Inc., Phoenix, Ariz.]
- Jordan, H. S. 1971. *Distribution of plutonium from accidents and field experiments*. LA-4756, pp. 21-24. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Jordan, H. 1981. Taped interview at Los Alamos National Laboratory, September 22, 1981.

- Kaye, S. V. and O. J. Nelson. 1968. Analysis of specific-activity concept as related to environmental concentration of radionuclides. *Nucl. Saf.* 9:53-58.
- Kaye, S. V. and P. S. Rohwer. 1970. *Dose-estimation studies related to proposed construction of an Atlantic-Pacific interoceanic canal with nuclear explosives: Phase III* ORNL-4579. Oak Ridge, Tenn.: U.S. Atomic Energy Commission.
- Kaye, S. V., P. S. Rohwer, K. E. Cowser, and W. S. Snyder. 1969. Predicting radiation dose equivalents for populations. I. Dose models and methods of application. *Bioscience* 19:238-41.
- Koranda, J. J. and J. R. Martin. 1971. Gamma-emitting radionuclides in Alaskan environments 1967-1970. In *Radionuclides in ecosystems*, ed. D. J. Nelson, CONF-710501-P1, pp. 81-107. Proceedings of the 3d national symposium on radioecology held in Oak Ridge, Tenn., May 10-12, 1971. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Krey, P. W. 1967. Atmospheric burnup of a plutonium-238 generator. *Science* 158:769-71.
- Langham, W. H. 1956. Determination of internally-deposited radioactive isotopes from excretion analyses. *Am. Ind. Hyg. Assoc. J.* 17:305-18.
- Langham, W. H. 1962. Radiation safety in the development and use of nuclear energy for rocket propulsion. *Health Phys.* 8:305-11.
- Langham, W. H. 1968. *The problem of large-area plutonium contamination*. Seminar paper 002. Washington, D.C.: Bureau of Radiological Health, U.S. Public Health Service.
- Langham, W. H., with editorial assistance of J. F. Becker. 1969. *Biological considerations of non-nuclear incidents involving nuclear warheads*. UCRL-50639. Livermore, Calif.: Lawrence Radiation Laboratory.
- Langham, W. H. 1971. *Plutonium distribution as a problem in environmental science*. LA-4756, pp. 3-11. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Langham, W. H. 1972. Trip report on foreign travel (October-November 15, 1971). Personal communication from Dr. Langham to the author.
- Lewis, F. 1967. *One of our H-bombs is missing*. New York: McGraw-Hill.
- Lotz, W. E. 1964. Symposium on inhaled radioactive particles and gases—Statement on the problem. *Health Phys.* 10:863-66.
- Martin, J. R. and J. J. Koranda. 1971. Recent measurements of cesium-137 residence time in Alaskan vegetation. In *Radionuclides in ecosystems*, ed. D. J. Nelson, CONF-710501-P1, pp. 108-15. Proceedings of the 3d national symposium on radioecology held in Oak Ridge, Tenn., May 10-12, 1971. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Martin, W. E. 1963. *Close-in effects of an underground nuclear detonation on vegetation. I. Immediate effects of cratering, throw-out, and glass*. Preliminary report from Project Sedan, PNE-228 P. Univ. of Calif. at Los Angeles.
- Martin, W. E. and S. G. Bloom. 1976. Plutonium transport and dose estimation models. In *Transuranium nuclides in the environment*, pp. 385-400. Proceedings of a symposium held in San Francisco, November 17-21, 1975. Vienna: International Atomic Energy Agency.
- Martin, W. E. and S. G. Bloom. 1977. Nevada Applied Ecology Group model for estimating plutonium transport and dose to man. In *Transuranics in natural environments*, eds. M. G. White and P. B. Dunaway, NVO-178, pp. 621-706. Las Vegas: U.S. Department of Energy.
- Martin, W. E. and F. B. Turner. 1965. *Food-chain relationships and radiostrontium in the Sedan fall-out field*. Project Sedan final report PNE-237 F. Univ. of Calif. at Los Angeles.
- Mason, B. J., K. W. Brown, H. W. Hop, and C. L. Miller. 1971. Desert vegetation uptake of tritium from Project Gasbuggy effluent. In *Radionuclides in ecosystems*, ed. D. J. Nelson, CONF-710501-P1, pp. 177-82. Proceedings of the 3d national symposium on radioecology held in Oak Ridge, Tenn., May 10-12, 1971. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- National Council on Radiation Protection and Measurements. 1984. *Exposures from the uranium series with emphasis on radon and its daughters*. NCRP no. 77, Bethesda, Md. NCRP. See National Council on Radiation Protection and Measurements.

- Nevada Operations Office. 1982. *Announced United States nuclear tests—July 1945 through December 1981*. NVO-209 (rev. 2), U.S. Department of Energy, Office of Public Affairs, in cooperation with Los Alamos, Lawrence Livermore, and Sandia National Laboratories.
- NVO. See Nevada Operations Office.
- Oak Ridge National Laboratory. 1972. *Environmental aspects of plutonium: A selected annotated bibliography*. ORNL-EIS-72-21. Oak Ridge, Tenn.: Oak Ridge National Laboratory. [Note: There were periodic comprehensive updates to this bibliography over the years of operation of the NAEG.]
- Oak Ridge National Laboratory. 1978. *Nevada Applied Ecology Group Publications*. ORNL/EIS-127. Nevada Applied Ecology Information Center. (NVO/AEIC-78/1, Nevada Operations Office.) Oak Ridge, Tenn.: Oak Ridge National Laboratory. [Note: This is indexed by name and by contributing organization.]
- Odland, L. T., R. G. Thomas, J. C. Taschner, H. R. Kaufman, and R. E. Benson. 1968. Bioassay experiences in support of field operations associated with widespread dispersion of plutonium. In *Diagnosis and treatment of deposited radionuclides*, eds. H. A. Kornberg and W. D. Norwood, pp. 256-65. Proceedings of the 7th annual Hanford biology symposium held in Richland, Wash., May 15-17, 1967. Amsterdam: Excerpta Medica Foundation.
- ORNL. See Oak Ridge National Laboratory.
- Robison, W. L. and L. R. Anspaugh. 1969. *Assessment of potential biological hazards from Project Rulison*. AEC report UCRL-50791. Berkeley, Calif.: U. S. Atomic Energy Commission.
- Rohwer, P. S., C. J. Barton, R. E. Moore, and S. V. Kaye. 1974. An evaluation of nuclear gas stimulation in terms of potential radiation exposure to the public. In *Proceedings of the 3d international congress of the International Radiation Protection Association*, ed. W. S. Snyder, CONF-730907-P2, pp. 1060-65. Held in Washington, D.C., September 9-14, 1973. Oak Ridge, Tenn.: Technical Information Center.
- Romney, E. M. and W. A. Rhoads. 1966. Neutron activation projects from Project Sedan in plants and soils. *Soil Sci.* 30:770-73.
- Romney, E. M., A. Wallace, and J. E. Kinnear. 1978. Plant uptake of Pu and Am through roots in Nevada Test Site soils. In *Selected environmental plutonium research reports of the NAEG*, NVO-192, vol. 1, pp. 109-20. Las Vegas: U.S. Department of Energy, Nevada Operations Office.
- Romney, E. M., A. J. Steen, R. A. Wood, and W. A. Rhoads. 1967. Concentration of radionuclides by plants grown on ejecta from the Sedan thermonuclear cratering detonation. In *Radioecological concentration processes*, eds. B. Åberg and F. P. Hungate, pp. 391-98. Proceedings of an international symposium held in Stockholm, April 25-29, 1966. Oxford-London-New York: Pergamon Press.
- Romney, E. M., A. Wallace, R. O. Gilbert, and J. E. Kinnear. 1976. $^{239,240}\text{Pu}$ and ^{241}Am contamination of vegetation in aged fall-out areas. In *Transuranium nuclides in the environment*, pp. 479-91. Proceedings of a symposium held in San Francisco, November 17-21, 1975. Vienna: International Atomic Energy Agency.
- San Diego Union. 1984. Nuclear excavation considered for Thai canal. Associated Press release in *San Diego Union*, November 23, 1984.
- Sanders, R. 1962. *Project Plowshare—The development of the peaceful uses of nuclear explosives*. Washington, D.C.: Public Affairs Press. [With foreword by Willard Libby.]
- Scheimer, J. F. and I. Y. Borg. 1984. Deep seismic sounding with nuclear explosives in the Soviet Union. *Science* 226:787-92.
- Seymour, A. 1979. Taped interview at Univ. of Wash., June 1, 1979.
- Seymour, A. H. and V. A. Nelson. 1977. Radionuclides in air, water, and biota. In *The environment of Amchitka Island, Alaska*, eds. M. L. Merritt and R. G. Fuller, pp. 579-613. Springfield, Va.: National Technical Information Service.
- Smith, D. D. 1978. Area 13 grazing studies—Additional data. In *Selected environmental plutonium research reports of the NAEG*, NVO-192, vol. 1, pp. 59-93. Las Vegas: U.S. Department of Energy, Nevada Operations Office.

- Smith, D. D. 1979. *Summary report of the grazing studies conducted on a plutonium-contaminated range in Area 13 of the Nevada Test Site*. EMSL-LV-O539-24. Las Vegas: U.S. Department of Energy, EPA Environmental Monitoring and Support Laboratory.
- Smith, D. D., J. Barth, and R. G. Patzer. 1976. Grazing studies on a plutonium-contaminated range of the Nevada Test Site. In *Transuranium nuclides in the environment*, pp. 325-36. Proceedings of a symposium held in San Francisco, November 17-21, 1975. Vienna: International Atomic Energy Agency.
- Stannard, J. N. 1973. Plutonium in the environment. Chapter 15 in *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh; pp. 669-88. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.
- Stead, F. W. 1964. Distribution in groundwater of radionuclides from underground nuclear explosions. In *Engineering with nuclear explosives*, TID-7695, pp. 127-38. Proceedings of the 3d Plowshare symposium, held April 21-23, 1964. Springfield, Va.: National Technical Information Service.
- Stewart, K. and R. H. Wilson. 1968. *Final evaluation of the biological measurements on Operation Roller Coaster (Joint US/UK field experiments)*. AWRE 0-76/67. Unclassified limited distribution. United Kingdom Atomic Weapons Research Establishment.
- Tamura, T. 1976. Physical and chemical characteristics of plutonium in existing contaminated soils and sediments. In *Transuranium nuclides in the environment*, pp. 213-29. Proceedings of a symposium held in San Francisco, November 17-21, 1975. Vienna: International Atomic Energy Agency.
- Teller, E., W. K. Talley, G. H. Higgins, and G. W. Johnson. 1968. *The constructive uses of nuclear explosives*. New York: McGraw-Hill.
- Thomas, R. G. 1981. Letter to R. H. Wilson, Univ. of Rochester, dated June 16, 1981.
- Thomas, R. G. and R. H. Wilson with assistance of B. B. Boecker, R. Lie, L. J. Siegneur, G. A. Smith, and J. L. Terry. 1959. *Field studies of fission product inhalation. Part III. Fission product field release test series one (FPFRT-I)*, UR-555. Rochester, N.Y.: Univ. of Rochester, Atomic Energy Project.
- Thomas, R. G., R. H. Wilson, G. A. Smith, and R. Lie. 1959. *Field studies of fission product inhalation. I. Fission product inhalation following an experimental in-pile meltdown*, UR-544. Rochester, N.Y.: Univ. of Rochester, Atomic Energy Project.
- Turner, F. B. 1963. *Influence of a cratering device on close-in populations of lizards*. Project Sedan report PNE-114 F (UCLA).
- Turner, W. D., S. V. Kaye, and P. S. Rohwer. 1968. *EXREM and INREM computer codes for estimating radiation doses to populations from construction of a sea-level canal with nuclear explosives*. K-1752, 193. Oak Ridge, Tenn.: Union Carbide Corporation, Oak Ridge National Laboratory.
- Turner, F. B. and W. E. Martin. 1964. *Food-chain relationships of iodine-131 in Nevada following the Sedan Test of July 1962*. Project Sedan report PNE-236 F (UCLA).
- U.S. Air Force. 1970. Project Crested Ice. Special edition of *USAF Nuclear Safety*. AFRP 122-1, vol. 65, pt. 2.
- Van der Hoven, I. 1960. A diffusion-deposition fallout model for the Kiwi-A reactor. Paper presented at the 187th national meeting of the American Meteorological Society held in Eugene, Oreg., June 15, 1960. [Dr. Van der Hoven was at the U.S. Weather Bureau Research Station, Las Vegas.]
- Wallace, A. and E. M. Romney. 1978. Has the work of NAEG at the safety shot sites come to a logical conclusion? In *Selected environmental plutonium research reports of the NAEG*, NVO-192, vol. 1, pp. 121-26. Las Vegas: U.S. Department of Energy.
- Wildung, R. E. and T. R. Garland. 1980. The relationship of microbial processes to the fate and behavior of transuranic elements in soils, plants, and animals. In *Transuranic elements in the environment*, ed. W. C. Hanson, DOE/TIC-22800, pp. 300-335. Springfield, Va.: National Technical Information Center.

- Wilimovsky, N. J. and J. N. Wolfe, eds. 1966. *The environment of the Cape Thompson Region, Alaska*. AEC report PNE-481, from Clearinghouse for Federal Scientific and Technical Information. Springfield, Va.: U.S. Department of Commerce.
- Wilson, R. A. 1959. *Field studies of fission product inhalation. II. Mobile field facilities*, UR-545. Rochester, N.Y.: Univ. of Rochester, Atomic Energy Project.
- Wilson, R. H. 1984. Letter to J. N. Stannard dated October 31, 1984. [I am indebted to Mr. Wilson for a careful review of chapter 14.]
- Wilson, R. H. and J. L. Terry. 1965a. Biological studies associated with a field release of plutonium. In *Inhaled particles and vapours. II.*, ed. C. N. Davies, pp. 273-90. Proceedings of an international symposium held in Cambridge, England, September 28-October 1, 1965. Oxford-London-New York: Pergamon Press.
- Wilson, R. H. and J. L. Terry. 1965b. *Plutonium uptake by animals exposed to a non-nuclear detonation of a plutonium-bearing weapon simulant. I. Field operations*, UR-644. Rochester, N.Y.: Univ. of Rochester, Atomic Energy Project.
- Wilson, R. H. and J. L. Terry. 1968. *Plutonium uptake by animals exposed to a non-nuclear detonation of a plutonium-bearing weapon simulant*. POR-2512 (WT-2512), Project 4.1 (Official use only). Washington, D.C.: Defense Atomic Support Agency.
- Wilson, R. H., R. G. Thomas, and J. N. Stannard. 1960. *Biomedical and aerosol studies associated with a field release of plutonium*, Test Group 57, Program 72 of Operation Plumbbob. Sandia Corporation Report WT-1511 (Univ. of Rochester Atomic Energy Project).

OUTLINE MOVEMENT OF RADIONUCLIDES THROUGH THE ENVIRONMENT

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Capsule Chronology^(a)

- | | |
|--------------------------|--|
| 1920s and earlier | Investigations of "dusty trades." Theories of atmospheric diffusion and dispersion developed. |
| 1930s | Further development of ideas regarding air transport as part of the field of industrial hygiene. |
| 1940s | Marked development of aerosol science and of meteorology. |
| 1950s | <p>Role of food chains in transfer becomes prominent. Windscale discharges into Irish Sea provide opportunities for tracing movement of radionuclides (see also chapter 11).</p> <p>Extensive studies of environmental transport of radionuclides reported from USSR.</p> <p>First environmental standards for radioactivity proposed, including water quality criteria.</p> <p>Research begins on resuspension phenomena.</p> |
| 1952 | Oak Ridge symposium demonstrates uses of isotopes in animal and plant nutrition research, also potentials for measuring environmental transfer. |
| 1955, 1958 | Ideas of recycling radionuclides in the environment and other aspects of environmental transport discussed at the two Atoms for Peace Conferences. |
| 1956 | First suggested contamination standard for plutonium (Los Alamos). |
| 1957 | Windscale fire in United Kingdom provides opportunity to follow environmental transfer of many radionuclides, especially iodine. |
| 1958 | Revised standards for surface contamination with plutonium implemented (Navy, Air Force). |
| 1960 | Chamberlain papers on aerosol behavior. |
| 1960s | <p>Pathway analyses gain in sophistication.</p> <p>Controlled Environmental Radioiodine Tests (CERT)^(b) at Idaho Falls.</p> <p>Much use of resuspension factors, critical pathways, and critical radionuclides.</p> |
| 1960-1969 | Peculiarities of arctic food chain transfer studied, especially in Norway, Sweden, USSR, Finland, Alaska, and Canada. |
| 1961 | Test Group 57 work (see chapter 14) incorporated into standards for plutonium surface contamination. |
| 1962 | UNSCEAR report discusses pathway analyses. |
| 1963 | <p>Iodine release from PUREX plant at Hanford provides another opportunity to check environmental transport (especially Soldat).</p> <p>Environmental pathways for iodine from nuclear tests reported in detail (UCLA).</p> |

(a) Many of the events pertinent to the subjects of this chapter have already been cited and will not be repeated here, unless of special importance.

(b) For abbreviations and acronyms, see Appendix D.

- Mid-1960s** Food chain transfer phenomena cause reduction in limits for effluents from light-water-cooled reactors by large factor (Appendix I of 10 CFR 50).
Modeling begins to grow rapidly.
- 1964** Federal Radiation Council introduces concept of Protective Action Guides (much more ERC in chapters 12 and 16).
- 1965** ICRP issues report with ideas of critical pathway, critical radionuclide, and critical population.
Auerbach discourses on recycling phenomena.
- 1967-1968** Series of LLL reports on environmental contamination due to fallout and the associated transfer phenomena.
- 1968** Cross-plume distribution factor (Slade).
Kathren reviews surface contamination levels for plutonium.
- 1969 et seq.** Whole-body-counter studies of body burden versus activity in foods, e.g., cesium in body versus milk (several laboratories). See also chapters 11 and 12.
- Late 1960s and early 1970s** Large increase in population dose assessments, all of which require knowledge of transfer phenomena and factors.
- 1970s** Work on concentration ratios for plant uptake from soils, also animal-plant concentration ratios.
Transfer from abiotic to biotic compartments studied in depth.
Burnett explains the "Factor of 700" used for Appendix I.
Controversy on deposition velocity factors.
Modeling gets increasingly sophisticated.
Several formulations developed for wind pick-up phenomena.
- 1971** Healy suggests decision levels for surface contamination (Los Alamos).
- 1971 et seq.** CUEX modeling methodology developed at Oak Ridge. Also INREM and EXREM computer codes, AIRMOD atmospheric model and TERMOD terrestrial model (Kaye, Rohwer, et al.).
- 1971-1973** The "Year-2000 Study" includes much on transfer factors.
- 1972** DASA report suggests three levels for surface contamination with plutonium.
Interim standard proposed for plutonium in soils (Healy at Los Alamos).
EPA guide for environmental surveillance issued.
Transformations of pollutants in water thoroughly described.
Book by Garner on transfer of radioactive materials.
Transuranic element transfer in the environment becomes a key study.
- 1973** Second edition of Eisenbud's book, *Environmental Radioactivity*.

- 1974** Idea of population dose commitment introduced as "Collective Dose Equivalent" at IAEA Portoroz seminar.^(a)
 EPA introduces concept of "Environmental Dose Commitment."^(a)
 HPS symposium on population exposures includes much on transfer functions.
 Environmental survey of the uranium fuel cycle.^(a)
 Safe Drinking Water Act.
- 1974-1975** Validation of ICRP Operational System.
- 1975** EPA standards for radioactivity in drinking water. Much discussion, especially of the radium standard.
 EPA draft environmental statement on normal operations of uranium fuel cycle.
 Reactor safety study (WASH-1400) contains much information on environmental transport.
 Study published on thirty years of environmental transport in White Oak Lake, Tennessee (Dahlman and Van Voris, Oak Ridge).
- 1976** EPA publishes drinking water regulations for radionuclides (40 CFR 141). Radon and uranium omitted.
 EPA hearings on 40 CFR 190.
 EPA issues draft statement on federal guidance for limits of plutonium in soils.
- 1977** ICRP introduces idea of collective dose equivalent.
 EPA document issued on radiological quality of the environment in the United States.
 Los Alamos report on pathways of plutonium from soil to man (Healy).
 EPA issues draft guidance on transuranic elements in the general environment.
- 1977, 1980, 1984** Reviews of resuspension factor work.
- 1978** Comprehensive review of movement of radiostrontium in soils and uptake by plants (Francis, Oak Ridge).
- 1979** EPA standards for uranium fuel cycle, Part A implemented (40 CFR 190).
 Interim soil limits suggested for D&D projects (Healy et al., Los Alamos).
- 1980** UNSCEAR gives detailed tabulations of ⁹⁰Sr transfer functions.
 EPA regulations (40 CFR 190) for uranium mills go into effect.
 EPA proposes clean-up standards for soil contamination (40 CFR 192).
 Discussion of EPA proposals for uranium in drinking water.
- 1980s** Modeling becomes an end in itself.

(a) Depended strongly upon environmental transfer factors.

- 1981 Actinide modeling tried.
- 1982 Publication of Whicker and Schultz's book on radioecology.
- 1983 Publication of Till and Meyer's book on radiological assessment.
Publication of proceedings of NCRP annual meeting on environmental radioactivity.
EPA regulations on active sites (40 CFR 192, parts D and E) become effective.
EPA regulations on uranium fuel cycle, Part B, go into effect (40 CFR 190); concerns ^{85}Kr and ^{129}I .
- 1984 Publication of NCRP report on radiological assessment.
Publication of Kathren's book on radiation in the environment.

Chapter 15

Movement of Radionuclides Through the Environment

Overview

The final chapter of this series of five on radionuclides in the environment considers some of the most complex phenomena of all—the quantitative description of transfer and the development of population dose assessment and standards for population exposure. The basic phenomena are only partly biomedical. Soil chemistry, aerosol physics, meteorology, and atmospheric processes play prominent roles among others, but the internal emitter establishment was deeply involved and worked closely with the other disciplines. Naturally, the chapter emphasizes the biomedical aspects, but there is, perforce, something of nearly everything.

The presentation does not follow a strictly chronological sequence. It was considered best to describe the major systems first, more or less in their present state, and then develop the chronology. Also, since the field is dominated by large compendia developed by government agencies and/or groups of laboratories, the presentations tend to be more anonymous, with less identification of individual investigators than many others in this book. Exceptions are in the earlier, simpler days. Nevertheless, a few institutions and a few individuals are mentioned so frequently that the reader can get a good idea of where the most concentrated areas of activity reside.

There is first a brief description of the major transport pathways, atmospheric, terrestrial, surface water, ground water, and dietary usage factors. This is followed by a general chronology of the development of the systems. The ideas of critical pathways, critical nuclides, and critical populations, and of recycling receive special emphasis. Modeling and the centers for development of modeling are considered next, followed by some highlights for specific radionuclides, e.g., strontium, cesium, iodine, and, as a unit, plutonium, the transplutonics, uranium, and thorium. In connection with cesium, the special phenomena of the arctic food pathway are described. In connection with iodine, the CERT tests at Idaho Falls are discussed in some detail since they have not been generally available. This is followed by an examination of the reduction factors introduced for pathways involving food and recycling of radionuclides that were the basis for Appendix I of the Code of Federal Regulations.

The chapter concludes with a review of population and environmental dose assessments and the development of standards for environmental media or based upon environmental phenomena. The latter include drinking water; the regulation of effluents from light-water-cooled reactors; standards for surface contamination, particularly for plutonium, as developed by the military; standards for contamination of soil; the uranium fuel cycle; and transuranium elements in the general environment. There is a separate section on resuspension and "the resuspension factor" because of the importance of resuspension phenomena in both evaluation and standard setting and extensive amounts of work done on them by all concerned. The gradual shift from occupational to population standards is described, along with some of the controversy that has surrounded the introduction of new very low guidelines by the Environmental Protection Agency.

Fortunately, the quantitative details have been very well described in recent comprehensive compendia, which are cited. Therefore, the chapter introduces only general mathematical relationships and examples of the final results but omits, partly to save space, some of the more complex intermediary processes of derivation. It should be obvious to the reader that this is a very dynamic aspect of the field of radionuclides in the environment and is full of portents for the future. To a degree, it represents a culmination of the research and field work chronicled in the first four chapters of this series on the environment and radionuclides.

I. The Setting

Throughout the pages concerned with observations and research on radionuclides in the environment, we have had occasion to note, in passing, various aspects of environmental transport. Here we will consider the origins and present status of the study of environmental transport processes in their own right and, in form, as much like an entity as can be managed for such a disparate field.

Research in this field has had a very broad base. Indeed, the setting is about as ecumenical as any facet of the saga of the radionuclides. Only the efforts of physicists and chemists in the production and isolation of the hundreds of new elements in the years of World War II and their collaboration with biomedical scientists toward understanding their modes of action and potential hazards had a comparably broad base. In the case of environmental transport, it was the industrial hygienists, aerosol physicists, meteorologists, hydrologists, agrologists and agronomists, oceanographers, and geologists who, in addition to biomedical scientists, supplied the broad base for the initial efforts. More recently, the field has added many varieties of computer scientists, systems analysis experts, and statisticians to become probably the most quantitatively sophisticated (and complicated) of all of the major areas of research on radionuclides. Only the most intricate facets of internal emitter dosimetry have similar claims on quantitative sophistication and, in this author's view, these complexities are less necessary than for the field of environmental transport.

The problems of environmental transport involve from a few to scores of variables. In the early days, rather simplistic analyses could be made by isolating a small segment of the system. With the growing capabilities of systems analysis, computerized calculations, and data storage, larger and larger segments of the environment have been folded in. Each step has involved from some to

considerable modeling, since only a few steps could be described in full without models. Thus, current research regarding environmental transport of radionuclides is rife with modelers and modeling. Indeed, it is a modeler's heaven, for the job cannot be done any other way. As can be expected, the basic scientific questions have sometimes been buried by the models, but fortunately the leaders in the field, at least as it has been applied to radionuclides, have been able to avoid serious excesses in this regard.

It has been suggested, probably by a tired transport modeler, that the calculation of the dose to humans at the end of the environmental transport chain may have more uncertainties than the transport chain itself. This seems most unlikely. The number of variables in the transport equations far outnumber those for ordinary dosage calculations. Their range of variation is as large if not larger. However, when we consider that environmental transport, as a field of endeavor, was essentially nonexistent for radionuclides (except for air transport) until the mid-1950s, whereas problems of dose calculations have been under investigation for much longer, it is surprising that the latter is still less than fully satisfactory (chapters 16 and 20).

Space prohibits any detailed recounting of the present status of the environmental transport field. Fortunately, we are blessed with very recent and adequate summaries that can provide interested readers with all they need to ascertain the present state of the art. Among these in the U.S. literature are the following:^(a)

1. R. J. Garner. 1972. *Transfer of Radioactive Materials from the Terrestrial Environment to Animals and Man*.
2. B. E. Vaughan et al. 1981. *Problems in Evaluating Dose via Terrestrial and Aquatic Pathways*.
3. F. W. Whicker and V. Schultz. 1982. *Radioecology: Nuclear Energy and the Environment*, especially chapter 5 in volume 1 and chapter 1 in volume 2.
4. NCRP. 1983. *Environmental Radioactivity*. Proceedings of the 19th Annual Meeting of National Council on Radiation Protection and Measurements, April 6-7, 1983.
5. J. E. Till and H. R. Meyer, eds. 1983. *Radiological Assessment: A Textbook in Environmental Dose Analysis*.
6. R. L. Kathren. 1984. *Radioactivity in the Environment: Sources, Distribution and Surveillance*.
7. NCRP. 1984. *Radiological Assessment: Predicting the Transport, Bioaccumulation, and Uptake by Man of Radionuclides Released to the Environment*.
8. D. Randerson, ed. 1984. *Atmospheric Science and Power Production*.^(b)

(a) Full references for each are in the bibliography.

(b) In addition to the above, the reader with access to Department of Energy (DOE) documents can find some very concise and very practical summaries in a series of reports from Battelle, Pacific Northwest Laboratories to DOE. Especially complete is a document, "Environmental Dose Assessment Methods for Normal Operations at DOE Nuclear Sites" by Strenge, Kennedy, and Corley (1982). This is part of a largely unheralded and unpublished comprehensive assessment of environmental doses from operations of DOE sites. The referenced report gives a brief review of available models for atmospheric transport and diffusion, waterborne transport, exposure pathways and dosimetry, followed by recommended models for the same parameters. This work is being continually updated to fit the committed dose equivalent concepts (chapter 16).

Several of these carry extensive lists of references. These, plus the symposia cited in chapter 11, the detailed references in chapters 12, 13, and 14, and the several International Atomic Energy Agency (IAEA) symposia to be cited further along in this chapter should meet any need for ascertaining facts.

Unlike most of the other major presentations in this book that could adhere fairly closely to the chronology of events, this subject requires a different approach. We will first introduce the systems more or less as they now exist and then return to trace, in part, some highlights of their development. Also, this field is rife with very large compendia and consolidated efforts of major laboratories or of government agencies. While individual investigators can be identified in the early phases, the literature beginning in the early to mid-1970s has tended to be more or less anonymous, or lists so many contributors to large efforts that it seems unfair to select out individuals without knowing exactly the extent of their contribution. It is clear that of the laboratories in the internal emitter establishment, Hanford, Lawrence Livermore, Los Alamos, New York University, and Oak Ridge were the most heavily involved. Also, recent years have seen the emphasis shift from laboratories to agencies of the government, primarily the Atomic Energy Commission (AEC) and its successor agencies (Energy Research and Development Administration [ERDA] and DOE), the Environmental Protection Agency (EPA), and the Nuclear Regulatory Commission (NRC), plus involvement of the Public Health Service (PHS) for more specialized aspects.

II. The Systems

We will examine briefly the major systems involved in the environmental transfer of radionuclides. They are reasonably obvious but should be set out since most of the analyses tackle primarily one or another of the major systems. They are: (1) the atmosphere and atmospheric transport; (2) terrestrial transport involving soils, vegetation, and animal products; (3) transport in surface waters; and (4) transport in ground water. The ultimate objective is, of course, assessment of the dose to humans. To accomplish this, an entire system of "usage factors" has been developed to apply to dietary and inhalation pathways. Some of this ties closely to dosimetry; e.g., lung model and gastrointestinal tract model, but, in general, the environmental scientists have been content to let their systems bring the radionuclide to the point of its entrance to the human body and let others take responsibility for the final dosage calculation.^(a)

A. Atmospheric Transport

This was the earliest system to be developed in depth. In the days before and during World War II and the early postwar years, it was occupational exposure that commanded center stage. Inhalation hazards were paramount. Ingestion in either food or water was (and is) ordinarily of much less importance for in-plant exposures. The field of industrial hygiene had already made a respectable start in the prewar years around problems of "the dusty trades." Furthermore, wartime research concerning the dispersion of chemical warfare agents had

(a) This distinction is fast breaking down since the environmentalists, understandably, become impatient waiting for someone else to supply estimates of the ultimate dosage to humans from the models they have constructed.

added sophistication to understanding of atmospheric transport, and meteorology had added to understanding of both micro-and macrophenomena. Thus, those concerned with the atmospheric transport of radionuclides had an organized and expanding sister field to tie into. Much of the early work, as well as research today, is applicable equally well to radioactive and nonradioactive materials.

Theories of atmospheric diffusion and dispersion were developed as early as the 1920s. By the time industrial hygiene was becoming a recognized field, reasonable pictures were available to apply to different conditions such as stable air, turbulent air, inversion conditions, lapse conditions, and to the effects of humidity, precipitation, and other factors. For local transport and dispersion, the so-called Gaussian plume model has been and is used extensively for radionuclides. Chapter 2 in Report No. 76 of the National Council on Radiation Protection and Measurements (NCRP) describes this three-dimensional model and six other model types with comments on the geographical scale, frame of reference, type of topography treated, etc. There is still greater detail and still greater generality in the chapter by Brenk, Fairbent, and Markee (1983) in the book by Till and Meyer. A diagram of the coordinate system for a Gaussian plume model is shown as figure 15.1. This model is used in all of industrial hygiene and health physics.

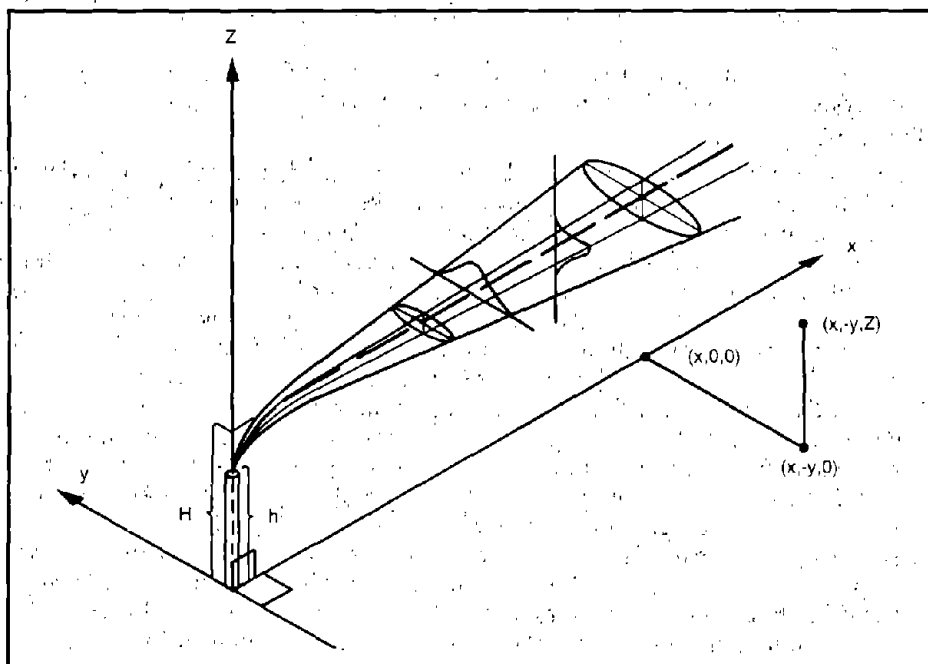


FIGURE 15.1. Coordinate system of the Gaussian plume model, showing distribution of concentration in the horizontal and vertical (after Turner 1969). (Derived from Turner 1969 as pictured in NCRP 1984. Reprinted with permission of the National Council on Radiation Protection and Measurements, Bethesda, Maryland, copyright 1984.)

It is interesting to note that many of the atmospheric transport models of later years are closely identified with, even named after, atomic energy installations. Among these are Hanford, Idaho Falls, Los Alamos, Oak Ridge, and Brookhaven National Laboratory in the United States; the aerosol physics and meteorology groups in England, cited in chapter 14; a group in West Germany (Klug, cited by Brenk, Fairbent, and Markee 1983); and many in the USSR. One reason for this development was the considerable pressure on nuclear energy installations from the very beginning to place special control on airborne releases when micrometeorological conditions were not favorable for rapid dispersion of the effluents. Also, the ease of measurement of radioactivity stimulated many tracer-type applications that involved the nuclear energy community still further.^(a) They were all tied together, however, by ideas and compendia by individuals such as Pasquill (1962, 1974) and contributions from AEC laboratories such as those by Gifford (1961, 1976) from Oak Ridge, the group at Hanford (Fletcher and Dotson 1971b; Soldat, Robinson, and Baker 1974), and Turner (1967) from the PHS. Also, the AEC air cleaning conferences cited in chapter 9 were valuable sources of information exchange (see also Slade 1968).

We must add, of course, that the demands of the research on fallout (chapter 12) stimulated greatly the involvement of the internal emitter community with problems of atmospheric transport on both a local and a global scale. A major portion of the AEC's expenditures on environmental sciences as late as fiscal year 1970 went for atmospheric radioactivity and fallout research (\$8.9 million versus \$6 million for terrestrial and freshwater ecology and \$4 million for marine sciences).^(b)

A few observations, chosen more or less at random, can serve to highlight some concepts and findings of the work on atmospheric transport not already cited in earlier chapters:

1. Several processes contribute to the transport and deposition of material in the atmosphere, not just air movement. These are pictured in figure 15.2, taken from Brenk, Fairbent, and Markee. It should be remembered from chapter 12 that the work on fallout from nuclear weapons tests showed that the bulk of deposition of radionuclides on a global scale came from the processes labeled "washout" and "rainout" in the above figure. By contrast, the deposition in arid climates such as the Nevada Test Site came from "dry deposition," except during the infrequent storms.
2. Much effort was expended on quantitating deposition. This began early, but we tend to associate radionuclide quantitation with studies on iodine. Some of these have been cited in earlier chapters, e.g., early studies at Hanford. The British did much of the basic work. A typical exposition appears in a summary by Chamberlain (1960), who worked at Harwell. This concerned primarily small particles. Other work considered larger particles and wet deposition as well as dry. The literature and models are replete with factors for velocity of deposition measured in centimeters per second. Much detail, but not much history, can be found in chapter 1 of volume 2 of Whicker and Schultz (1982). A recent review by Jones (1984) concerning the Atmospheric Modeling Working Group of the U.K. National Radiation Protection Board indicates that the field is still very active in nuclear energy circles.

(a) All of this was well before the days of the environmental impact statement!

(b) These figures quoted from Whicker and Schultz (1982), vol. 1, chapter 1.

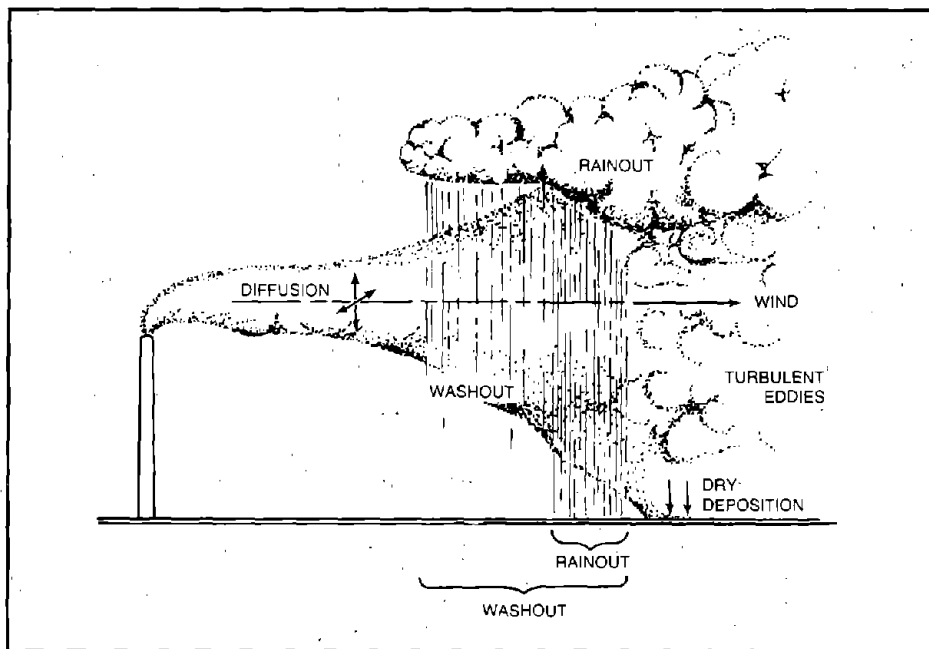


FIGURE 15.2. Atmospheric dispersion and removal processes. (Redrawn from Brenk, Fairbent, and Markee 1983.)

3. The importance of resuspension by wind of particles already deposited on the surface and attempts to quantitate it have occupied the attention of several laboratories in the AEC-ERDA-DOE fold. Indeed, they require a separate description that will be reserved for later discussion (section IV B) in this chapter.
4. Of particular interest in the atomic energy field, but by no means limited to it, is work on the influence of buildings on the air flow over and around them. Typical Gaussian plume kinetics, are illustrated in figures 15.2 and 15.3. These can be badly distorted close to a building, as illustrated in figure 15.4A and B. It is now part of the lore of practical health physics to measure rather than to predict concentrations of airborne radionuclides in such situations.

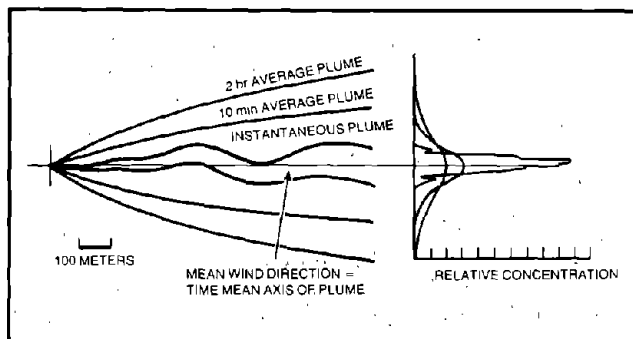


FIGURE 15.3. Gaussian transport. The diagram on the left represents the approximate outlines of a smoke plume observed instantaneously and of plumes averaged over 10 min and 2 hr. The diagram on the right shows the corresponding cross-plume distribution patterns (Slade, 1968). (From Brenk, Fairbent, and Markee 1983.)

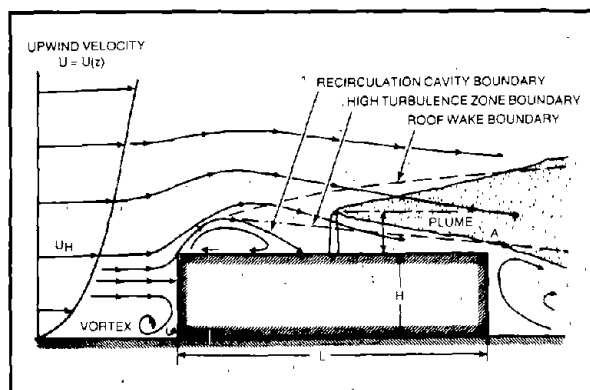
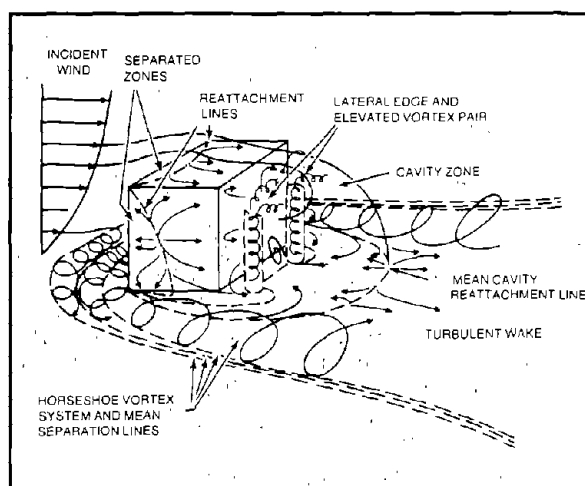


FIGURE 15.4A. (Left) Flow over center of a long, flat building roof for wind perpendicular to the upwind face. (Redrawn from Wilson 1979.)

FIGURE 15.4B. (Right) Model of flow near a sharp-edged building in a deep boundary layer. (Redrawn from Hosker 1979. Further details can be seen in Brenk, Fairbent, and Markee 1983.)



5. The emphasis in study of airborne transport of radionuclides has gradually shifted. In the years of World War II and until the problems of fallout took over, in-plant measurements for development of occupational exposure data were the primary objective. They still are for plants with potential inhalation hazards. But the potential for an inhalation exposure via the environment from releases of fission products or radioactive gases commanded attention. As the work on fallout progressed, the potentially much greater importance of the food pathway for population exposures emerged. The system thus became a two-step one. It considered first the airborne component and then the uptake directly or indirectly into food and the eventual transfer to humans via food.

During the past thirty years, the AEC-ERDA-DOE organization has taken a lead in synthesizing available knowledge on atmospheric transport processes. Its third major reference work, *Atmospheric Science and Power Production*, cited at the beginning of this chapter (Randerson, 1984) provides extensive information on current topics that are outlined in note 1 at the end of this chapter. It is clear that efforts to understand atmospheric transport processes, even those

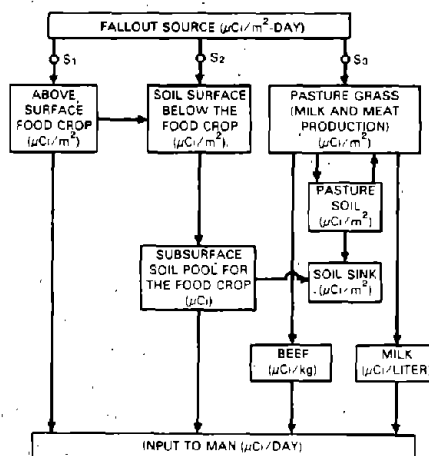
related to radionuclides, have been very broadly based and not so much an exclusive function of the biomedical community as was true for some of the other environmental areas. Yet, it has been the persistent need for hazard evaluation that, except for pure meteorology and aerosol science (see chapter 9), provided the prime stimulus. It is obvious from perusal of the bibliographies of some of the recent summaries that government is now providing much of the stimulus for the enterprise and that it resides significantly in the radiation protection community. A table in NCRP Report No. 76 (1984) gives a list of nineteen Gaussian models. The developers are distributed as follows:

U.S. Environmental Protection Agency(a)	12
State Environmental Protection Agencies	3
Oak Ridge National Laboratory	1
Lawrence Livermore Laboratory	1
Private Industry	2

B. Terrestrial Transport

Terrestrial transport of radionuclides involves living organisms as transporters as well as final recipients in contrast to atmospheric transport. A major role is played by vegetation, as is obvious from our earlier consideration of the forage-cow-milk-human pathway and others (chapters 12 and 13). A block diagram of terrestrial food pathways considered in one model (Booth and Kaye 1971) is shown as figure 15.5.

FIGURE 15.5. Block diagram of the terrestrial food pathways. (Modified from Booth and Kaye 1971. The symbols used in the detailed model have been deleted. Redrawn from NCRP 1984. Reprinted with permission of the National Council on Radiation Protection and Measurements, Bethesda, Maryland, copyright 1976.)



Even this relatively simple model, which does not attempt to break down the soil into various subcompartments, for example, has twelve transfer coefficients to be evaluated in addition to three source terms (S_1 - S_3) that represent deposition on above-the-surface food crops, on soil surface below the food crop, and foliar deposition on pasture grass. Obviously, while the source terms are indicated as from fallout sources (broadly speaking) and are, therefore, airborne, the source can also be waterborne, thus adding further transfer terms. Note also that factors such as the decay time in milk or beef, and the relative amounts in various parts of the beef, such as bone versus muscle, must be factored in to get meaningful input to humans. These are not shown in this particular model.

(a) By outside contracts in many cases.

There are models to represent transient contamination, such as from a pulsed event, and models for steady state conditions.

Some further insight into the many factors that need consideration in terrestrial food pathway models can be gleaned from the following:

If water is the source of the contamination by drinking, irrigation, etc., we need to know—

- concentration of radionuclide in water,
- concentration factor (accumulation factor) from water to plant or animal, directly or in sequence,
- drinking rate if drinking water is the primary source,
- soil accumulation by irrigation,
- soil accumulation by rainout,
- deposition on foliage by irrigation.

If air is the primary source of contamination, we need to know—

- the several deposition factors outlined above,
- the concentration of radionuclides in air,
- the particle size distribution in air,
- soil accumulation from air,
- if inhaled, the breathing rate and factors for lung deposition and retention,
- concentration factors (accumulation factors) in plant or animal directly or in sequence.

If feed is the primary source, we need to know—

- decay between times of deposition and of harvest,
- fraction translocated from soil to grain or forage,
- decay during storage of feed and thus knowledge of time between contamination and harvest, harvest and consumption, etc.,
- losses in home and commerce.

Factors of importance in the recipient are—

- daily ingestion of each component, e.g., milk, eggs, beef,
- secretion coefficient to milk,
- coefficient of transfer to meat or eggs,
- concentration in each component,
- pharmacokinetics within the body.

Small wonder that elaborate computer programs are needed to encompass even the major transfer factors. Small wonder too that there are many models and many computer programs to accommodate various facets of so broad an input.

We have already seen that soil-plant relationships are very dependent on the chemical composition of the incoming nuclide and of the soil and the conditions of growth. Further factors must be introduced for the duration of retention on leaves, the time between contamination and intake, etc. Details of how these factors are currently used can be found in the key summaries of Till and Meyer (1983), NCRP (1984), and Whicker and Schultz (1982).

In these models, the concentration ratio between plant and soil comes into serious use. Remember (chapters 12 and 13) that values for these were derived largely from greenhouse experiments with confirmatory numbers from field experiments and from the sites of nuclear tests.

Despite the apparently large amount of information accumulated, current modelers have had many occasions to use "default values," i.e., values

prescribed for a model parameter in the absence of data directly relevant to the assessment situation. A range of such default values for eight important radio-nuclides is given in table 15.1.

TABLE 15.1. Range of Default Values of B_{iv} , the Concentration Ratio for Plant Uptake from Soil, F_{im} , the Transfer Coefficient to Cow Milk, and F_{if} , the Transfer Coefficient to Beef^a

Element	B_{iv} ^b Conc. in Wet Vegetation/ Conc. in Dry Soil	F_{im} d L ⁻¹	F_{if} d kg ⁻¹
Co	1×10^{-3} to 9.4×10^{-3}	5.0×10^{-4} to 2.0×10^{-3}	1×10^{-3} to 1.7×10^{-2}
Sr	1.7×10^{-2} to 1.0	8.0×10^{-4} to 2.4×10^{-3}	3.0×10^{-4} to 2.0×10^{-3}
Ru	3.8×10^{-3} to 6.0×10^{-2}	5.0×10^{-7} to 1.0×10^{-6}	1.0×10^{-3} to 4.0×10^{-1}
I	2.0×10^{-2} to 5.5×10^{-2}	6.0×10^{-3} to 1.0×10^{-2}	2.9×10^{-3} to 2.0×10^{-2}
Cs	6.4×10^{-4} to 7.8×10^{-2}	5.0×10^{-3} to 1.2×10^{-2}	4.0×10^{-3} to 3.0×10^{-2}
Ra	3.1×10^{-4} to 6.2×10^{-2}	2.0×10^{-4} to 8.0×10^{-3}	2.0×10^{-4} to 3.4×10^{-2}
U	2.9×10^{-4} to 2.5×10^{-3}	1.2×10^{-4} to 6.0×10^{-4}	1.6×10^{-6} to 5.0×10^{-3}
Pu	1×10^{-6} to 2.5×10^{-4}	2.5×10^{-8} to 2.0×10^{-6}	4.1×10^{-7} to 5.0×10^{-3}

^aReferences: Fletcher and Dotson (1971a), Baker, Hoenes, and Soldat (1976), NRC (1977), CEA/NRPB (1979), Moore et al. (1979), McDowell-Boyer and Baes (1980).

^bValues for forage crops and edible portions of food crops.

Source: Modified slightly and reset from NCRP 1984, p. 13. References have been added to the bibliography. Reprinted with permission of the National Council on Radiation Protection and Measurements, Bethesda, Maryland, copyright 1984.

Note that the ranges of the default values are seldom much more than a factor of ten, except for plutonium.^(a) Note also the variety of models referenced to gather the figures shown in table 15.1.

In the U.S. NRC Regulatory Guide 1.109 (NRC 1977), plant-soil concentration ratios are given for thirty-one elements of importance in the nuclear fuel cycle. They range (pCi/kg vegetation ÷ pCi/kg soil) from 5.5×10^0 for carbon to 1.7×10^{-4} for zirconium.^(b) These seldom exceed unity and most indicate discrimination against the metal between soil and plant. This stands in marked contrast to concentration factors in aquatic media that may be very large (Kathren 1984, and earlier chapters) and indicates that transfer is, in general, a selective and idiosyncratic process.

Transfer rates, of course, play a major role in determining these factors. In table 11.4 in chapter 11, we saw that the degree of food-chain transport could

(a) The reason for this greater range may lie in the greater demands that plutonium places on analytical techniques and its tendency to shift valence states in different environmental situations.

(b) Iron is given as 6.6×10^{-4} . This must refer to an insoluble form of iron in the absence of chelators and perhaps in the ferric form.

vary widely among radionuclides. Thus, any transport models for terrestrial systems need to be nuclide-specific to be in tune with present-day requirements. In dealing with mixtures, the old practice of selecting "critical nuclides" can still be applied to some extent (more later) if one is careful.

Concentration ratios from plants to animals are equally element specific. A tabulation prepared by members of the Nevada Applied Ecology Group (Reichle, Dunaway, and Nelson) was reproduced by Whicker and Schultz (1982) and is shown as table 15.2.

TABLE 15.2. Animal/Plant Concentration Ratios for Selected Elements in Terrestrial Ecosystems

Element	Invertebrates			Mammals		
	Sapivores	Herbivores	Carnivores	Herbivores	Omnivores	Carnivores
Ca	0.1 - 18	0.1	0.1			
Sr		0.1	0.1	0.5 - 4.5		
K	3.5	3.0	2.0			
Cs	0.2	0.3 - 0.5	0.1 - 0.5	0.3 - 2.0	1.2 - 2.0	3.8 - 7.0
Na	17	21	27			
Co		0.4	0.5	0.3		
Ru		0.4	1.2	0.4		
Fe				0.8	0.2	
H	0.6			0.6		
P	11	17	18			
Ra				0.01		
I				0.5	0.2	0.1

Source: Reset from Reichle, Dunaway, and Nelson, *Nucl. Saf.* 11, p. 43, 1970 (via Whicker and Schultz 1982, vol. 2, p. 64).

These figures have many problems despite their apparent erudition. As Whicker and Schultz (1982, p. 63 of vol. 2) point out, it is difficult to determine even such simple things as whether or not the basis for the values was wet or dry weight and in many instances the exact plant-food base. Also, these are presumed to be average whole-body contents and would differ for different tissues in the same organism.

Nevertheless, the data illustrate an important point, sometimes the content of the animals is somewhat higher than that of the plants eaten. This is especially notable for elements like potassium, sodium, and phosphorus, whose concentrations in the animal body are regulated homeostatically.^(a) Also, it appears that there are not only differences among elements but some differences between major groups of animals (note, for example, cesium).

(a) Calcium is, of course, also rigidly regulated but happens to be lower in animals than in plants except for some sapivores.

Not all parameters are dependent on the nuclide concerned. In addition to those factors mentioned earlier we can cite:

- crop yield,
- weathering half-life,
- surface density of dry soil,
- build-up time in soil,
- fraction of time cattle are on pasture versus stored feed,
- area that animals, particularly cows, can be considered as utilizing (measured in m^2/day).

We can conclude that terrestrial transfer may be the most complex of those systems requiring analysis. At least it may require the most terms.

C. Surface Water Transport^(a)

This system concerns the transport of radionuclides discharged directly into surface waters as liquid effluent releases, deposition directly from the atmosphere, introduction via run-off from terrestrial deposits or the gradual introduction from ground water transport. The problems of river transport are very different from those of small ponds. Lakes are different from small ponds, and, of course, oceans are different from them all. Estuaries are a unique mix requiring specific treatment. Nevertheless, all of these differ from terrestrial transport (except air dispersion) by having a much higher degree of mobility and mixing over very wide areas.

At least two dichotomies appear. The first is the presence of potential for sizeable external radiation doses from radionuclides in the water, especially if they have been concentrated by biological activities. (Remember the high doses from organisms on the hulls of ships in the Bikini tests, seen in chapter 12?) This is in addition to the usual potential for intake by drinking the water or eating aquatic biota. The second dichotomy is between bottom sediments and the overlying water. Many insoluble radionuclides become attached to particles descending to the bottom, or concentrate in the sediments simply because normal mixing brings them into contact, or they eventuate there after becoming part of the shell or body of an aquatic organism. More soluble forms may remain in solution and circulate for long periods. Thus, we expect to find the transfer factors in aquatic systems very nuclide specific, as they are in terrestrial systems. We can also expect large differences in the biota depending on their feeding habits, e.g., bottom feeders versus others.

All of this became apparent in the work around the sites (chapter 11), in the studies in the Pacific (chapter 12), in laboratory and controlled field research (chapter 13), and in general aquatic ecology.

Biota play a prominent role in transport in surface waters. They may move appreciable quantities of radionuclides, particularly in the oceans and larger lakes where plankton form a considerable part of the biomass. However, it is via the food pathways that biota play their key role in aquatic systems. Food web models, one for ^{137}Cs in a freshwater environment, one for a more generalized web in a lake system, are shown in figure 15.6A and B.

(a) We are including here all aquatic systems that are not underground but obviously excluding the slowly exchanging marine waters below the thermocline.

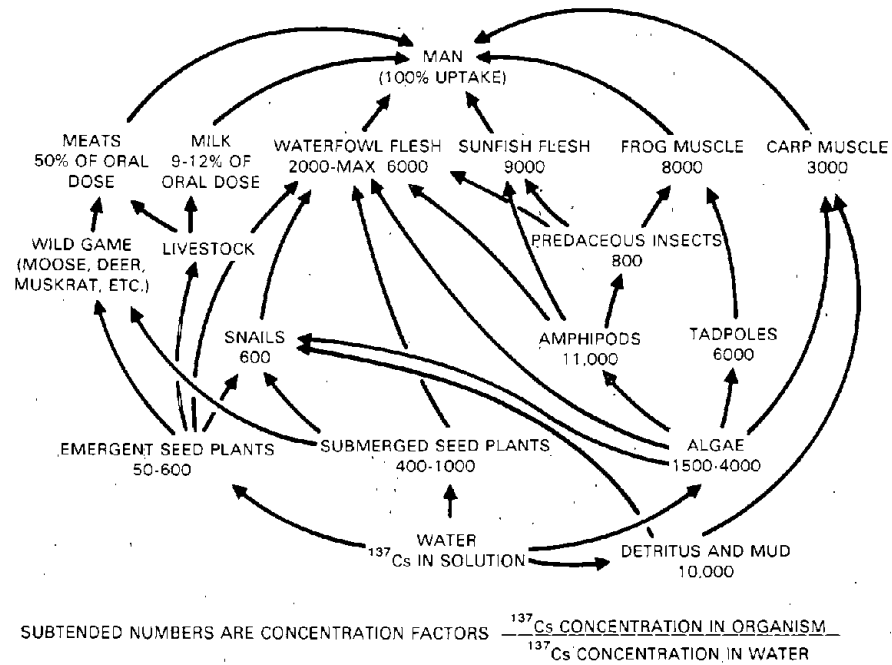
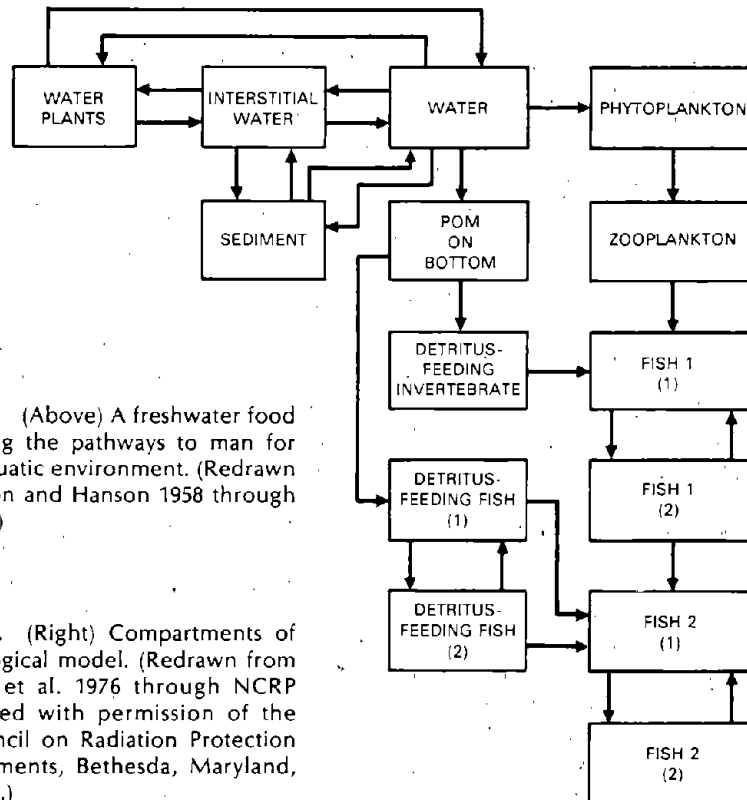


FIGURE 15.6A. (Above) A freshwater food web illustrating the pathways to man for ^{137}Cs in the aquatic environment. (Redrawn from Pendleton and Hanson 1958 through Peterson 1983.)

FIGURE 15.6B. (Right) Compartments of the lake ecological model. (Redrawn from Vanderploeg et al. 1976 through NCRP 1984. Reprinted with permission of the National Council on Radiation Protection and Measurements, Bethesda, Maryland, copyright 1976.)



Concentration (accumulation) factors in the aquatic environment are given in figure 15.6A. They illustrate again the point made earlier that such factors can be very high due, in part, to the very low concentration of radionuclides in the surrounding medium. A listing of concentration factors for over two dozen radionuclides in aquatic plants, crustaceans, mollusks and fish is given by Peterson (1983) in his monumental chapter on terrestrial and aquatic food chain pathways in the book by Till and Meyer. This is followed by a similar tabulation for estuaries and saltwater organisms.^(a)

Despite the emphasis we in biomedical science place on the role of biota, it is quite possible for hydrographers and physical oceanographers to spend entire careers on the physical and chemical transport processes alone. Jirka et al. (1983) list the following transport and transformation processes that affect radionuclide migration and fate in surface waters, none of them involving the biota:

Transport

- water movement
- discharge-induced advection and diffusion
- ambient advection and diffusion
- sediment movement

Intermedia transfer

- adsorption and desorption
- precipitation and dissolution
- volatilization

Degradation and decay

- radionuclide decay

Transformation

- production of daughter products

Even further detail of the many nonbiological processes that must be considered is shown in figure 15.7. This concerns the processes in what is commonly referred to as a water column, a much-worked concept in aquatic ecology and oceanography.

Obviously, much of this physicochemical work has been done by people we have not met elsewhere in this book. Nevertheless, it is surprising to find how many of the institutions familiar to us from efforts at dose assessment and evaluation of health effects have taken part in these aspects also. It has been an area for physical and biological scientists to rub elbows to a considerable extent. The interchange is needed, for all factors must be entered into the models.

D. Transport in Ground Water

The problems of radioactive waste disposal focused more attention on transport of substances in ground water than had ever occurred before. It is true that hydrologists were aware of the basic characteristics of ground water movement and its storage in geological formations or groups of formations known as aquifers. It was known that the movement of ground water could be very slow

(a) While we are accustomed to expect high concentration factors in freshwater systems because of the low concentrations of salts in freshwater, these tables show many values for marine organisms that are equally high.

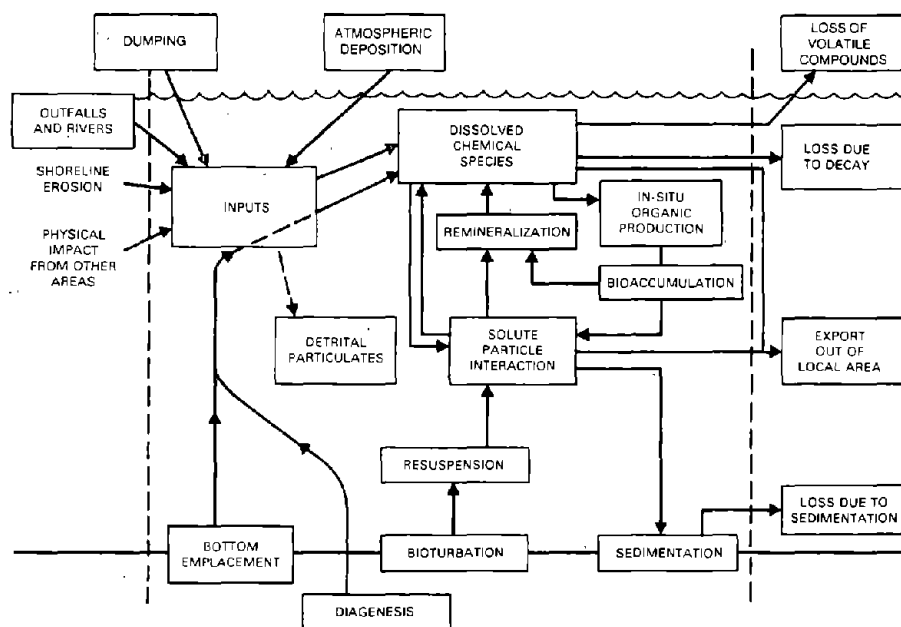


FIGURE 15.7. Possible transformations of a pollutant in the water column. (Redrawn from NOAA 1979 and NCRP 1984. Reprinted with permission of the National Council on Radiation Protection and Measurements, Bethesda, Maryland, copyright 1984.)

indeed, except for the presence of fissures or fractures that might generate underground streams. Nevertheless, the concern over possible movement of radionuclides from the early disposal sites, such as those at Hanford and Oak Ridge, led to much increase in study and financial support for this branch of environmental science. The findings have, of course, spilled over into assessment of the movement of chemical pollutants from disposal sites throughout the world.

Ground water transport problems differ from those we have examined thus far, not only in the slowness of movement but in the time spans to be considered. Because of the long half-lives of some components of radioactive waste (as well as the near-infinite half-lives of stable elements from chemical wastes) the time scale for making predictions can extend to thousands of years.

The role of biota in ground water transport is minor compared to terrestrial and surface water systems: Many volumes have been written and many blue-ribbon committees and symposia have been gathered to address the problems of waste disposal. Except for some surprises as to which radionuclides appear to assume controlling importance as the waste decays over the millennia, this work has not contributed very directly to the main theme of this book. To conserve space, it will be given only brief coverage. A review of some of the factors that enter into equations for the movement of ground water and ground water models will serve to summarize:

1. Tracers, either deliberately introduced or entering from already extant sources, ground water dating,^(a) and mathematical models have been used effectively.
2. Ground water flow can be represented by a set of coupled equations (Codell and Duguid 1983; Codell and Schreiber 1978).
3. Dispersion and diffusion in porous media, including molecular diffusion, can be estimated by entities such as porosity and effective porosity, dispersivity of tracers in different media, adsorption coefficients and distribution coefficients in different media, etc.
4. The models are numerous and complex but can be validated by measurements from existing or newly driven wells or similar means except for the deeper portions of the ground water system. Thus, much field work, is required. Pure laboratory research has less meaning than in the case of either terrestrial or surface water systems.

Sophisticated quantitative descriptions can be found in the chapter by Codell and Duguid (1983), in chapter 4 of NCRP 1984, and more qualitative considerations in the enormous literature on waste disposal (see, for example, Matuszek 1983). It might have been expected that the movement of radionuclides in ground water would be less nuclide-specific than in some of the other systems. However, the difference in chemistry of different soil types combined with differences between elements makes for notable differences in entities such as distribution coefficients. Examples can be seen in table 15.3A and B.

TABLE 15.3A. Distribution Coefficients:^(a) Strontium and Cesium^a

Material and Conditions	K_d (mL g ⁻¹)	
	Sr	Cs
Basalt, 32-80 mesh	16-135	792-9520
Basalt 0.5-4 mm, 300 ppm TDS ^b	220-1220	39-280
Basalt—0.5-4 mm, sea water	1.1	6.5
Basalt-fractured in situ measurement	3	—
Sand, Quartz - pH 7.7	1.7-3.8	22-314
Sands	13-43	100
Carbonate, greater than 4 mm	0.19	13.5
Dolomite, 4000 ppm TDS	5-14	—
Granite, greater than 4 mm	1.7	34.3
Granodiorite, 100-200 mesh	4-9	8-9
Granodiorite, 0.5-1 mm	11-23	1030-1080
Hanford Sediments	50	300
Tuff	45-4000	800-17800
Soils	19-282	189-1053
Shaley siltstone greater than 4 mm	8	309
Sandstone, greater than 4 mm	1.4	102
Aluvium, 0.5-4 mm	48-2454	121-3165
Salt, greater than 4 mm, saturated brine	0.19	0.027

^aTaken from Isherwood (1981).

^bTotal dissolved solids.

(a) The coefficient is the quantity sorbed divided by the quantity in ground water.
Source: Modified from NCRP 1984, p. 183. Reprinted with permission of the National Council on Radiation Protection and Measurements, Bethesda, Maryland; copyright 1984.

(a) A parcel of ground water will have lower and lower concentrations of atmospheric radionuclides the longer it has been in the ground.

TABLE 15.3B. Distribution Coefficients: Thorium and Uranium^a

K_d (mL g ⁻¹)	Conditions
—Thorium—	
160,000	Silt loam, Ca sat. Clay, pH 6.5
400,000	Montmorillonite, Ca sat. Clay, pH 6.5
160,000	Clay soil, 5 mM Ca(NO ₃) ₂ , pH 6.5
40-130	Med. sand, pH 8.15
310-470	Very fine sand, pH 8.15
270-10,000	Silt/clay, pH 8.15
8	Schist soil, 1 g/liter Th, pH 3.2
60	Schist soil, 0.1 g/liter Th, pH 3.2
120	Illite, 1 g/liter Th, pH 3.2
1000	Illite, 0.1 g/liter Th, pH 3.2
<100,000	Illite, 0.1 g/liter Th, pH >6
—Uranium—	
62,000	Silt loam, U(VI), Ca sat., pH 6.5
4400	Clay soil, U(VI), 5 mM Ca(NO ₃) ₂ , pH 6.5
300	Clay soil, 1 ppm UO ₂ ²⁺ , pH 5.5
2000	Clay soil, 1 ppm UO ₂ ²⁺ , pH 10
270	Clay soil, 1 ppm UO ₂ ²⁺ , pH 12
4.5	Dolomite, 100-325 mesh, brine, pH 6.9
2.9	Limestone, 100-170 mesh, brine, pH 6.9

^aTaken from Isherwood (1981).

Source: Reset from NCRP 1984, p. 184. Reprinted with permission of the National Council on Radiation Protection and Measurements, Bethesda, Maryland, copyright 1984.

E. Dietary Pathway Usage Factors

The final feature of the systems we have been considering is a fine illustration of the fact that there are few things that are not sooner or later pertinent to the evaluation of the health effects of radiation. Obviously, it does little good to know transfer factors and amounts of various radionuclides in various media, particularly food, without knowing how the intake is partitioned. It started in dosimetry calculations using the lung model, gastrointestinal tract model, etc., as defined in International Commission on Radiological Protection (ICRP) Reference Man (originally "Standard Man").^(a)

More recently, a concerted effort has been made to establish dietary usage factors for infant, child, teen, and adult. There was, of course, some necessary work done in connection with the global fallout studies—largely by the AEC Health and Safety Laboratory and the PHS (later EPA). In 1970, Durbin, Lynch, and Murray at Lawrence Berkeley Laboratory (then Lawrence Radiation Laboratory) did a thorough research on milk and mineral intakes of infants. They used balance studies from many laboratories, including the University of California. The changes with time over the critical first ten months to a year are, of course, considerable. This compendium, more like the product of a large governmental laboratory than a small academic group, is full of important detail, including intakes of calcium, phosphorus, potassium, and calculations for ⁹⁰Sr.

(a) See chapter 16.

In general, the necessary information was gathered by the cognizant government agencies, either directly or by contracts. It has now devolved upon the NRC.

Much has depended on data from a few sources, e.g., Rupp (1980); Rupp, Miller, and Baes (1980); Blanchard (1978); the National Marine Fisheries Service; and older references in the ICRP Reference Man report (see chapter 16).

A contemporary view of Reference Man was presented by Poston (1983) as a chapter in the book by Till and Meyer. A succinct summary of the usage factors for predicting exposures to man was provided in chapter 5 of the NCRP report (1984). The dietary usage factors were based primarily on market basket surveys, plus investigation of family composition and habits. They included "best estimates" for average daily intake of various foods by age group, relative frequency of consumption of various types of milk, age factors, sex factors, regional comparisons, and others. A kind of listing of default values for the average individual and for the maximally exposed individual is contained in the cited NRC Regulatory Guide. Such listings are shown as table 15.4A and B.

TABLE 15.4A. Values for Dietary Usage Factors from Regulatory Guide 1.109 to be Used for the Average Individual in Lieu of Site Specific Data^a

Pathway	Child	Teen	Adult
Fruits, vegetables & grain (kg y ⁻¹)	200	240	190
Milk (L y ⁻¹)	170	200	110
Meat & Poultry (kg y ⁻¹)	37	59	95
Fish (kg y ⁻¹) ^b	2.2	5.2	6.9
Seafood (kg y ⁻¹) ^c	0.33	0.75	1.0
Drinking Water (L y ⁻¹)	260	260	370

^aFrom NRC (1977).

^bFish includes freshwater and marine.

^cSeafood includes aquatic invertebrates.

Source: Modified slightly and reset from NCRP 1984, p. 199. Reprinted with permission of the National Council on Radiation Protection and Measurements, Bethesda, Maryland, copyright 1984.

TABLE 15.4B. Values for Dietary Usage Factors from Regulatory Guide 1.109 to be Used for the Maximum Exposed Individual in Lieu of Site Specific Data^a

Pathway	Infant	Child	Teen	Adult
Fruits, vegetables & grain (kg y ⁻¹)	—	520	630	520
Leafy vegetables (kg y ⁻¹)	—	26	42	64
Milk (L y ⁻¹)	330	330	400	310
Meat & Poultry (kg y ⁻¹)	—	41	65	110
Fish (fresh or salt) (kg y ⁻¹)	—	6.9	16	21
Other Seafood (kg y ⁻¹)	—	1.7	3.8	5
Drinking Water (L y ⁻¹)	330	510	510	730

^aAdapted from NRC (1977).

Source: Reset from NCRP 1984, p. 199. Reprinted with permission of the National Council on Radiation Protection and Measurements, Bethesda, Maryland, copyright 1984.

Note that these are suggested *for occasions when site-specific data are not available*. In the current regulatory climate, it is suspected that few installations would have the patience to gather their own data or the temerity to use it, unless the situation was really unique.^(a)

The need for knowledge of dietary habits must extend also to animals. French (1967) pointed out, for example, that the amount of ¹³¹I ingested by a small herbivorous animal may be as much as fifty times greater than a comparably sized granivore. The more or less unique position of the ruminants was emphasized in earlier chapters and by Garner (1972, p. 44).

There is no doubt that the generation of information on dietary usage has been important. It began during the furor over fallout (chapters 12 and 13). It has been continued ever since in the hands of a few conscientious and meticulous individuals, and under the auspices of institutions that saw the need for some of their research to be aimed at problems with less glamor than description of the latest nuclear particle. The data will find use in fields far removed from the environmental transfer of radionuclides, but we can thank the internal emitter establishment for doing it.

F. Commentary

It should be obvious from the description of the systems developed to describe environmental transport that hundreds of decisions need to be made for the parameters used in the more sophisticated models. The summaries emphasized in the discussion above were done by thoughtful investigators who went out of their way to emphasize the uncertainties of the models and to identify ways to validate predictions made by the models. It is abundantly clear that uncertainties abound.

Just how large these uncertainties may be when the models are used in a predictive mode is summarized by Vaughan et al. (1981), in material provided to the NAS-NRC FREIR Subcommittee II and here reproduced from the abstract of their subsequently published review:

This review is concerned with exposure risk and the environmental pathway models used for predictive assessment of radiation dose. Exposure factors, the adequacy of available data, and the model subcomponents are critically reviewed from the standpoint of absolute error propagation. Although the models are inherently capable of better absolute accuracy, a calculated dose is usually overestimated by from two to six orders of magnitude, in practice. The principal reason for so large an error lies in using "generic" concentration ratios in situations where site specific data are needed.

Major opinion of the model makers suggests a number midway between these extremes, with only a small likelihood of ever underestimating the radiation dose.

... The extremely wide errors associated with predicting exposure stand in striking contrast to the error range associated with the extrapolation of animal effects data to the human being.

Further research must concentrate on reducing these. It is unlikely that anyone will be injured because of these uncertainties, since the more conservative choices have been made at nearly every turn. It does seem likely that totally unnecessary costs and procedures will add to the furor and apprehension about

(a) For example, Windscale (chapter 11), the Marshallese (chapter 12).

radioactivity in the environment if inappropriate models or improper parameters are used. Worse yet is the potential for slavish adherence to some model because it received the official blessing of a regulatory agency. There is still much to be learned about an entity as complex as our environment. Furthermore, the authors of the best summary documents consistently urge against use of a complex model if a simple one will suffice.

In our present situation, we can get far from reality unless those using the systems are aware of the genesis and background of what we now have.^(a,b) We will spend much of the balance of this chapter on historical development of our present points of view. These cannot be traced as inexorable pathways from early trials to present practices. We do not have space for that, nor could it be done with any ease. Yet, it is hoped that some of the connections will be apparent. Many have been described, in part, in earlier chapters.

III. Genesis of the Systems

A. General Development

The chronology of research on transfer factors involving radionuclides in the United States is comparable to that of radioecology reviewed in chapter 11. It began at Hanford. The pioneer work on the Columbia River was aimed more at effects than cycling, at the outset, but quantitation of transfer factors came out

- (a) Good discussions of the limitations of transport models can be found in Whicker and Schultz (1982, vol. 2, chapter 1) and Garner (1972). The latter emphasizes the need for having data from a field study or studies. The former enumerates the uncertainties in some detail and points out that, while it is customary to use "deterministic" transport models (i.e., specific single values are used as input), an alternative is the probabilistic or stochastic model where the inputs are frequency distributions. Of particular importance is the view emphasized by Garner that a highly sophisticated model does not always make for a more accurate assessment no matter what the input data. Some additional models that might interest the reader are one for milk from contaminated pastures by Lengemann (1970) at Cornell; of cesium from fallout to milk by Wilson, Ward, and Johnson (1969) at Colorado State; for strontium and cesium in the human food chain by Aarkrog (1971) in Denmark; and an important comparison of observed versus theorized capacities of the environment for radioactive contaminants by Foster (1973) at Pacific Northwest Laboratory.
- (b) *Note Added in Proof:* We have eschewed any attempt at details of the modeling, except to illustrate the processes involved. As modeling grew, the suggested values for input parameters likewise proliferated. Indeed, two authors using the same basic model could get different results based on their selection of the input parameters. To provide some guidance, or at least information, on practices used by the calculators, DOE stimulated a unified compilation of models and parameters considered appropriate for assessing the potential or actual impact of radioactive discharges to the environment (Miller 1984). This was done in the Dosimetry and Biological Transport Section of the Health and Safety Research Division of Oak Ridge National Laboratory, an organization with much experience in internal dose calculations, as we have seen. It compares exposure pathways; gives models for each of the major pathways outlined in this chapter, along with their components; and provides conversion factors for external dose-rate as well as estimates of committed dose equivalent for internal exposures, doses, or dose equivalents resulting from atmospheric releases of tritium and carbon. It also includes sample calculations. This is a most useful document.

came out as sort of a bonus. There was, in addition, pioneer work on the waste disposal sites, and some of the earliest reports of airborne contamination of the environment came from the Hanford Works. While the river work has wound down with the closing of most of the reactors, the waste disposal sites continue as sources of data. Even in the 1980s, work on "U Pond" on the Hanford reservation continues. We associate the names of Foster, Davis, Hungate, Healy, Nakatani, Hanson, Bustad, and Kornberg with the earlier reports (to name a few) and vehicles such as the Hanford classified reports, progress reports, and publications in the Atoms for Peace Conferences, the national symposia on radioecology, the symposium on Radioisotopes in the Environment in 1960, and an ever-growing crescendo from that point on.^(a)

In 1963, long after the Hanford program in environmental sciences had become lusty, there was an accidental release of 60 Ci of ^{131}I from the PUREX (plutonium and uranium recovery through extraction) Chemical Separations Plant. This brought on the scene a name we have long associated with environmental transfer of radionuclides and the development of modeling, Joseph K. Soldat. In a 1965 paper, Soldat gives a useful vignette of how contamination and transfer problems in that acute release incident were handled. Soon Soldat established himself and his group and Hanford's Pacific Northwest Laboratory (PNL) as a generator of environmental transfer models (see, for example, Soldat 1971).

The Oak Ridge work was largely focused on waste disposal. It did not involve as large a geographical area as Hanford, but, as we saw in chapter 11, it went many miles down the Clinch and Tennessee River systems. The early efforts at Oak Ridge are associated primarily with names like Auerbach, Krumholz, Struxness, Park, and, behind the scenes, Karl Morgan, who spearheaded the fight for support. These were soon joined by Kaye, Dunaway, Olson, Nelson, and more recently, Rohwer.

In due course, the other operating sites, e.g., Savannah River, brought in still different milieu. Eventually, each installation, including each nuclear power plant of the present day can, and some have, added to our information on environmental transfer factors.

Information gained from the experiences surrounding fallout from nuclear weapons tests made invaluable contributions to our knowledge of environmental transfer mechanisms and quantitative data for transfer factors. Global fallout rained indiscriminately on land and sea, and the local fallout from the Pacific tests was, much of it, deposited in the sea. The excellent work by oceanographers and aquatic biologists was added to information already gathered around the sites regarding aquatic transfer processes. However, it was in the area of terrestrial transfer that the fallout situation contributed the most new knowledge. We have traced its development, especially at and around the Nevada Test Site (NTS) and in the Pacific islands, in earlier chapters.

We should mention again that the British contributed much to the early development of the field by their work around Windscale, through both the routine discharges into the Irish Sea and the accidental atmospheric release in October 1957.

(a) A good review of the entire process can be seen in the book by Kathren (1984).

B. Biological Availability^(a)

In the early 1970s, it was becoming evident that there was no "right" way to determine the value of the all-important transfer factors that are ubiquitous in dose assessment models. The problem was that of choosing which one of several different orders of magnitude best represented the transfer ratio, e.g., of ^{90}Sr from soil to plant, or, of ^{241}Am from soil to plant. Indeed, in these cases, published transfer ratios were found to vary over at least three orders of magnitude (Vaughan, Wildung, and Fuquay 1976). In 1971, Price critically reviewed several hundred references of interest in nuclear waste management (Price 1971), eventually retaining 119 reports illustrative of this wide range for any given radioelement. It was clear that neither soil type, plant type, nor soil profile distribution fully explained the differences reported, and experimental artifacts had been ruled out.

At this point, Raymond Wildung, working in the Ecosystems Department of PNL, entered upon a long series of studies on the soil microbial and geochemical processes that underlie soil-to-plant transfer phenomena. He and his colleagues took an operational concept—the transfer ratio—and placed it on a definitive chemical and biochemical basis.^(b) These contributions can be better understood, as can the driving need for using site-specific data, by quoting from the review by Vaughan et al. (1981):

Only a very small fraction of radioelements bound to soils or aquatic sediments are available to biota, but this fraction is variable over a wide range. The concept of biological availability rests on several lines of evidence, but it has been systematized only in the soil/plant system: i.e., (1) ligand formation enhances plutonium uptake and translocation in plant and animal systems (Watters et al., 1980); (2) the small fraction of heavy metals in soils that is actually exchangeable closely reflects soil amendment fractions (Cataldo and Wildung, 1978); and (3) the factors controlling availability are both exogenous and endogenous. Exogenous factors may involve such source term variables as valence state of the radioelement, its molecular form, concurrent presence with chelates or other exogenous complexation agents, and particle size, as discussed earlier. Endogenous factors may involve ligand metabolites of soil microflora and plant roots, and geochemical factors determined by soil characteristics. Similar processes undoubtedly operate in sediment/microflora/detritivore systems of lakes and streams. Related processes may operate also in organism-to-organism transfer of plutonium through sequential food chains; e.g., gastrointestinal absorption of ligand-bound plutonium is significantly enhanced over the inorganic forms of plutonium subject to hydrolysis (Wildung et al. 1979).

At present, the chemical basis for biological availability deals mainly with plutonium (Watters et al., 1980) and heavy metals (Cataldo and Wildung, 1978). One may expect that similar processes will be common to any radioelement whose chemistry is primarily controlled by hydrolysis or whose electron configuration favors complex ion formation. Among the long-term or large radiological contributors to dose, this includes isotopes of uranium, plutonium, and americium in the actinide series; strontium, cesium, and cadmium; and nickel, iron, and cobalt in the transition series. Complexation with soluble ligands may maintain the solubility of several of these elements, and thus compete with their sorption to soil and sedimentary

(a) This section was supplied by Dr. Burton E. Vaughan, PNL.

(b) Dr. Wildung received the E.O. Lawrence Award in 1982 in recognition of these contributions and advancement of our understanding of the environmental behavior of plutonium.

particles. Such reactions do not necessarily increase their biological availability from [soil solution or] the water column; i.e., larger complex ions may not be biologically absorbable whereas the small ones may be. Clearly, a great deal depends on the type of polymer or complex ion formed, which in turn is a strong function of chemical and biological properties of particular [media] . . .

One very pragmatic corollary of these investigations is that exogenous contaminant will be much more biologically available than the same element as an endogenous constituent of soil. This has been proven for many heavy elements by use of soil amendment procedures (Cataldo and Wildung 1978). Most of the endogenous elements present in soil are simply unavailable to green plants—a greatly overlooked point. The concern about enhanced biological availability is by no means restricted to soil processes. As indicated above, enhanced gastrointestinal absorption of plutonium has been observed when the plutonium was present as an organically bound plant ligand.^(a)

C. Critical Pathways, Critical Nuclides, Critical Populations

In the chapter on fallout, we became aware of the need to select, very early in the work, certain radionuclides as “critical.” The entire spectrum of fission products was, of course, far too extensive to attempt detailed study of every one.

The ICRP is usually credited with formalizing the simplifying concept of selecting certain pathways and populations, as well as nuclides, for primary attention and designating them as “critical.” Committee-4 of ICRP developed a report on environmental monitoring (ICRP 1965) that recommended concepts and procedures for such monitoring.^(b) Since there are a few nuances of language that are important, let us quote from the ICRP’s comments on their recommendations:

The exposure of an individual is a function not only of the levels of radiation and radioactivity in his environment, but also of the individual’s use of that environment and of his personal habits. The Commission recognized this difficulty in paragraph 39 of ICRP Publication 6, and suggested a procedure for assessing and controlling individual exposures. This procedure involves studying a sample of the exposed group and setting the environmental level so that no individual in the sample receives any excessive exposure. This method has sometimes been used satisfactorily, but has proved somewhat arbitrary, especially when the exposed group contains individuals with a wide range of habits.

Most installations which handle radioactive materials are designed and operated to contain the radiation and radioactive materials, and to concentrate their by-product wastes. Nevertheless, some release of radioactivity to man’s environment occurs, due either to the disposal of low activity wastes or to accidents. The releases are made to many different sectors of the environment and the amounts and compositions of the releases will vary from installation to installation (even between installations of the same general type) and from time to time.

- (a) [We saw in chapter 13 that there are, for some radionuclides at least, solubilization processes that occur over relatively long periods of residence. This was particularly noted when the element had been through several uptakes and harvests. This does not conflict with the statement made above concerning greater availability of exogenous contaminant.]
- (b) It will be recognized that some of them were already in use. The concept of critical group was reiterated in ICRP Publication 9 (ICRP 1966).

Thus, in most situations in which radioactive materials are introduced to man's environment, there will be numerous and complex pathways by which each of the released nuclides may ultimately cause radiation exposure of man. An example of such a pathway is the deposition of strontium-90 on grazing land, its direct retention on grass or its uptake into the grass from the soil, its ingestion by cows and the subsequent ingestion of cow's milk by people, especially children. Further examples are given in Appendix A. A comprehensive and detailed study of all such pathways will not be needed, even for installations which involve potential radiation hazards of the greatest magnitude, e.g. reactors, reactor fuel reprocessing plants and stores of fuel reprocessing wastes. Experience has shown that a study of the situation will indicate that certain nuclides and certain exposure pathways are much more important than others. These nuclides and pathways are designated "critical."

The presence of a critical nuclide in some critical pathway will not cause the same exposure of each member of the population outside an installation, and preoperational investigations will usually establish the existence of one or two groups of people whose characteristics, e.g. habits, location, or age, cause them to receive doses higher than those received by the rest of the population outside the installation and thus require them to be considered separately, i.e. to be designated as critical. Great judgment is necessary in defining such a group in practice and the following aspects will have to be considered. Some of these are the same as the factors influencing the design of routine surveys and only those concerned with the critical group itself are listed below:

- (a) The location and age distribution of the potentially exposed group.
- (b) Dietary habits, e.g. special foodstuffs and amounts consumed.
- (c) Special occupational habits, e.g. the handling of fishing gear.
- (d) The type of dwelling, e.g. shielding characteristics.
- (e) Domestic habits, e.g. time spent indoors, frequency of personal washing and laundering of clothes.
- (f) Hobbies, e.g. sport fishing or sunbathing.

Such groups in the population may be in the vicinity of the installation or at some distant location; they may include adult males, adult females, pregnant women, and children; they may be individuals who eat foodstuffs prepared in a special way or produced in a particular location; or they may be people who work in a particular industry. Only general guidance can be given on the considerations needed to define the critical group and the associated critical nuclides and pathways, for the situation will be specific for each installation and its environment, but the importance of such a definition is considerable. The concept of the critical group provides a sound and practical way of complying with the Commission's recommendations concerning members of the public. It also allows economies in the conduct of environmental monitoring.

The critical group should be identified in such a way that it is representative of the more highly exposed individuals in the population and is as homogeneous as practicable with respect to radiation dose, that is, with respect to those factors which affect the dose in the specific case considered.

Once a critical group has been identified in this way, a suitably representative sample of the group should be selected and studied so as to assess their actual or potential exposure. The average exposure of such a sample should then be regarded as typical of that of the highly exposed individuals and the Commission's recommendations for the maximum permissible doses for individual members of the public applied to that average. The spread of values in the sample will give some measure of its homogeneity with respect to the characteristics which have been studied. It must be recognized that there are many characteristics of the individual (such as metabolic rates) which may influence the dose received and which are not measured. These individual differences may tend to increase the spread of

the individual doses received within the critical group. It must also be recognized that, outside the critical group, there may be a few individuals whose habits and characteristics are dramatically unconventional. Such peculiarities may sometimes mean that these individuals receive doses somewhat higher than those to the critical group. It is expected that methods of waste management will be determined not by the possible exposure of these individuals but rather by the dose to the critical group. (ICRP Publication 7, 1965, references and cross-references omitted.)

The ICRP points out that this procedure departs slightly from the idealized aim of not allowing any single individual to receive more than the upper limit of dose but views the procedure as coming reasonably close to this objective. They also point out the then-current limitations of standard man (Reference Man, chapter 16) and suggest use of idiosyncratic data if necessary.

A simplified diagram of the more likely pathways was presented as an Appendix to the ICRP report and is reproduced as figure 15.8A and B.

FIGURE 15.8A. Simplified diagram of potential critical pathways to man for radionuclides released to ground or surface waters (including oceans). (Modified from ICRP 1965. Reprinted with permission of Pergamon Press, Elmsford, New York, copyright 1965.)

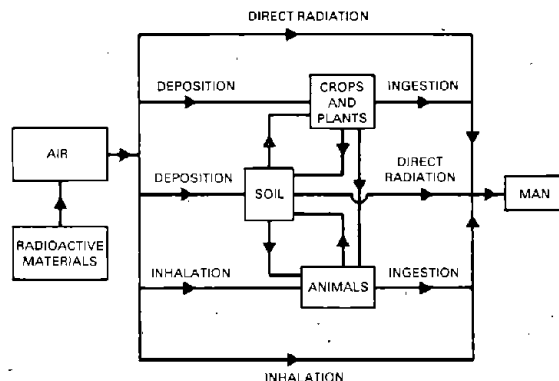
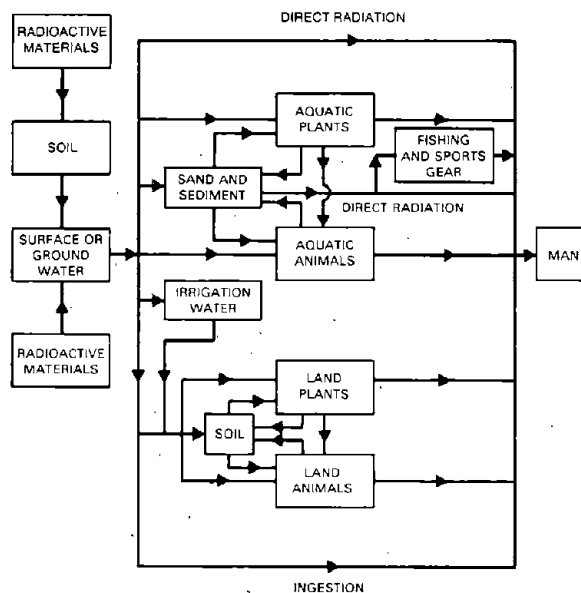


FIGURE 15.8B. Simplified diagram of potentially critical pathways to man from radionuclides released to the atmosphere. (Redrawn from ICRP 1965. Reprinted with permission of Pergamon Press, Elmsford, New York, copyright 1965.)

In a wide-ranging discussion of criteria for the control of radioactive effluents given at an earlier IAEA symposium, Morgan and Struxness (1971) present a slightly expanded description of the ICRP critical group idea:

The critical group in the population is that group of individuals relatively small in number and reasonably homogeneous that is considered to receive the largest dose to critical body organs and/or to receive the greatest damage from the radioactive contamination. Some of the facts which must be considered in selecting this critical group are location and age distribution, dietary habits, special occupational habits, type of dwelling and heating equipment, domestic habits, hobbies, etc. The critical group may for example be limited to males, females, pregnant women or children of a given age. It may be individuals who eat certain types of food, religious groups that follow certain customs or persons with certain illnesses which affect their habits or metabolism. In any case, it is recognized that due to individual variability there will always be some spread in the dose received within such a critical group in spite of the fact that it is relatively homogeneous from practical considerations. The Commission allows half of the members of this critical group to exceed its dose limits in that the average dose of the critical group may be equal to but not greater than the dose limits given in column 3 of Table VIII. It recognized further that there will always be some members in a large population which have peculiar habits which markedly enhance radionuclide uptake, for example, an individual who may obtain a large fraction of his food from fish soup in which the bones as well as the flesh of the fish are consumed. In such cases the doses he receives may be considerably greater than the recommended dose limits even though the ICRP's recommendations are complied with in that the average dose received by the critical group does not exceed these limits. This recommendation of ICRP is perhaps less restrictive than the AEC Regulations. (Morgan and Struxness 1971, pp. 225-226)

Further along we find important practical advice:

The ICRP has indicated that it usually is not necessary to carry out very extensive environmental monitoring at reactor and isotope facilities, but in preplanning and in subsequent studies to confirm the accuracy of calculations and the safety of an operation, it is essential that a number of various types of measurements be made to assure that the critical segment of the population has been properly identified and that no factors of reconcentration have been overlooked. (Morgan and Struxness 1971, p. 227)

Buried in the long and detailed discussion by Morgan and Struxness (p. 221) is the following:

Since any worthwhile enterprise of man is possible only by accepting certain inherent risks, the nuclear energy industry probably is no exception. The choice, therefore, seems to be between these relatively small hypothetical risks of the nuclear energy industry and the very real risks of power shortages or a smog polluted environment and the associated respiratory diseases we might expect from fossil fueled power plants.

A sound philosophy for 1970 and just as sound for the present, when perspective seems ever more elusive. It will be recognized that the diagrams in figure 15.8 depict only very general pathways. These did seem to be sufficient for the original objectives of the ICRP plan. For more sophisticated applications, a more finely tuned system was needed to feed into the developing computer codes. For example, if ingestion was determined to be the critical pathway, which one was critical? Was it animals to humans or plants to humans? Was it plants to animals to humans? Was it a product of animal activity such as milk? If it was the grain pathway, what grain? Any of these could be "critical" for different radionuclides and for different circumstances.

More difficult than the designation of critical pathway in practice was the designation of the critical group. Sometimes, as we have already seen with the

laverbread eaters around Windscale, the critical group in the population may be small, yet their presence may control an entire operation. Indeed, the British apparently did control to the single individual with the highest potential exposure before ICRP 7 was published (Preston, Mitchell, and Jeffries 1974).^(a,b)

The selection of critical nuclide can be made site-specific, but, for general environmental contamination, it can follow much the same course described in chapter 12 for choosing which of the thousands of radionuclides produced in fission should be concentrated upon. The United Nations Scientific Committee on the Effect of Atomic Radiation (UNSCEAR 1962) judged potential importance of radionuclides by the following:

- production yield and half-life (as described in chapter 12);
- date of entry into food chains after deposition on earth's surface;
- extent of entry into foods of animal origin, such as milk;
- extent of absorption from the gastrointestinal tract and time of retention in man;
- fraction deposited in critical organ and time of retention therein.

On this basis, essentially the same line-up of radionuclides came out at the final step, i.e., receipt by humans, as in the early days of the characterization of fallout. In addition, tritium and krypton were studied carefully, not because of their potential toxicity (see earlier chapters), but because of their mobility in the environment. They could thus be used as what I will term "marker-nuclides" since they may signal the movement of contamination along a path. In addition, some shorter-lived radionuclides (^{89}Sr , ^{140}Ba , and especially ^{131}I) can potentially be critical soon after release.

An examination of how well the ICRP operational system was working or might work came, in part, in work by Preston, Mitchell, and Jeffries (1974) and a companion study by Beach (1975) of the U.K. National Radiological Protection Board. Preston and Jeffries (1969) looked in depth at the critical exposure pathway around Windscale. They did exhaustive analyses of the sources of raw material for the laverbread, its production, distribution, and marketing, a job that suited well the capabilities of the Fisheries Radiobiology Laboratory at Lowestoft where they worked. They chose a critical group of adults in line with ICRP-9 recommendations (children were shown to receive a lower dose) and assumed they derived their laverbread entirely from the source of highest cesium concentration, viz., Cumberland. The estimated doses were from 0.4 to 0.7 rem/yr to the lower large intestine during the period 1962-1967. Since the dose limit to individual members of the public recommended by the ICRP was 1.5 rem/yr, and the assumptions were very conservative, they could conclude (although they did not do so overtly) that the system was working. The later

- (a) While the critical group was fairly carefully described by ICRP, the characteristics of a "suitable sample" (see quotation) seem to have been left more or less loose. Presumably these evaluations would always have the benefit of competent statistical advice, but it appears that intuition may have had to play a role in many instances. Perhaps we should not decry this, for no serious mistakes seem to have been made. It may be one of the last times unbridled intuition could compete with computers.
- (b) *Note added in proof:* Hunt and Shepherd from the United Kingdom (1980) expanded considerably on identification of critical groups and have, to a degree, negated the hiatus in ICRP recommendations mentioned in the preceding footnote. They give several alternative methods for selection.

study (Preston, Mitchell, and Jeffries 1974) did not measure or calculate radiation dose. It focused on identification of the critical group and concluded that unless there were at least eighty observations made "the result will be based on less than two known individual's habits" and that the exceptional individual may well control, despite the formality of choosing a group.

The work by Beach (1975) considered radiation doses. The consumption rate of laverbread was measured along with the radioactivity of the *Porphyra* from which it was made. This established a critical group size, viz., thirty, and from this they estimated that the annual collective dose to the lower large intestine of the laverbread consumers was 266 man-rem.

In a panel discussion at the New York symposium already cited (see Morgan and Struxness 1971), Herbert Parker (Battelle) asked about the probability of there being significant undetected critical pathways. This touched on one of the constant worries of the ICRP's approach and brought several answers. E. E. Pochin (United Kingdom) described the increasing scale of whole-body-counter studies and the efforts to find sites of long-term retention of radionuclides that might have been overlooked. He opined that the only chances for a surprise were with low concentrations and long retention of isotopes with long physical half-lives.

L. Rogers from the AEC's Division of Reactor Development described broad studies of several operating reactors being done by the Environmental Health Service of the U.S. Department of Health, Education and Welfare (PHS) to identify *all* radionuclides in the environment and detect any unexpected concentrations. None were found.

A. Preston (United Kingdom) remarked on the surprise they got concerning the increasing amounts of cesium in effluents from Magnox power stations. It had developed during long burn-up times of the fuel and was not anticipated in the first estimates. Hence, the admonition was made to keep measuring and checking and not assume that nothing new will turn up in nuclides, pathways, or populations during the operation of a facility, no matter how carefully planned.

Despite the possibilities, it seems unlikely that the critical pathway-nuclide-population approach missed important events. However, like the critical organ approach for dosimetry, which has now been abandoned by ICRP, the act of choosing may require choices between nuclides, pathways, or groups that are of quite comparable importance. Thus, contributions of close competitors may be neglected. Indeed, the contributions of several such could exceed those of a single "critical" choice. These situations may be the primary drawback of the original ICRP approach. Doing many pathways is no problem for the sophisticated systems of the present that allow simultaneous calculations for several pathways, several nuclides, and several populations.

Throughout the years of application of the critical pathway approach, and despite the implication that individual operators and modelers should try to be very site specific, the regulatory atmosphere did little to encourage such originality. As a result, the calculations for practical use tended to be largely generic and were individualized only for very special cases. Very recently, Bernard Cohen, University of Pittsburgh, has checked on the merits of an alternative approach to pathway analysis for transport of elements from soil to human diet (Cohen 1985).

This alternative approach used only the average daily ingestion of each element and its abundance in soil, i.e., \bar{I}/C_s where \bar{I} is the average daily ingestion of

element X by the U.S. population and \bar{C}_s is its average concentration in U.S. soil. The results were compared to those obtained by the more complex pathway analysis system. They were consistent with each other within a mean factor of four, "which is roughly the standard deviation in estimates from the pathway analysis." This confirms the intuitive feeling that many have held that we may have become too elaborate in our application of pathway analysis. However, more work and the reaction of the environmental establishment is needed before such conclusions can be drawn firmly. Cohen points out that each method has important advantages in some applications.

D. Recycling

The idea of a critical pathway implies or subsumes, even though the ICRP did not state it overtly, a straight line, "once-through" mechanism. Very early in the development of radioecology it became apparent that cycling and recycling of radionuclides (as well as stable elements) were integral and important parts of the ecosystem processes. Recurrent transfers occur between ecosystems and within the components of a given ecosystem. Sometimes the end result was referred to as "reconcentration" and was a cause for concern, as we saw at the end of the quotation from Morgan and Struxness on page 1285. A very adequate description of the basic phenomena, including mathematical descriptions of the processes, is given in the book by Kathren (1984, pp. 251-254) under the heading "Biological Turnover."

Auerbach (1965) points out that the facts of recycling emerged from at least four lines of investigation: (1) analyses based on the movement of fallout radionuclides at different trophic levels, (2) tracer experiments done to elucidate links in food chains, (3) studies of rates of turnover of specific nuclides within a single trophic level, and (4) tracer experiments done with complete cycles within an ecosystem. The early work was described at the two Atoms for Peace Conferences, the symposium on radioecology at the University of Minnesota, the early U.S. national symposia on radioecology (all cited in chapter 11), and the fourth Hanford biology symposium entitled "Radiation and Terrestrial Ecosystems" held in 1965 and listed along with other Hanford symposia in chapter 8. Historical development is described also by Mitchell (1974) and courses through most of the review by Auerbach just cited. We will see a few further details when we consider specific pathways.

Rice (1965), referring to cycling of radionuclides in the marine environment, emphasized that:

Each radionuclide takes a characteristic route and has its own rate of movement from component to component prior to coming to rest in one of the three components of the marine environment [solution or suspension, sediments, or biota]. Plants and animals to be of any significance in the cycling of radionuclides ... must accumulate the radionuclide, retain it, be eaten by another organism and be digestible. (Rice 1965, p. 953)

Auerbach goes out of his way (1965, p. 1356) to emphasize that the cycling process is considered to regulate and to maintain ecosystems "in a steady state within particular climatic and physiographic zones." A corollary is that errors can be made if transfer factors or other quantitative parameters are deduced from a system that is not in a steady state. Frequently, as with local fallout or single contaminating events, there is no chance of a steady state existing. This

does not mean that pathways cannot be mapped, only that due cognizance must be taken of the situation. It has been.

An obvious way to handle the cycling problem is to break the system down into compartments between which transfer takes place. Thus, the familiar fallout forage-cow-milk-human pathway was analyzed, as we saw for ^{90}Sr in chapter 12, compartment by compartment. However, in the setting of standards and other regulatory operations, a single factor representing the entire pathway may be employed. This has grown out of the mountains of work all over the world already alluded to. In using any single factor, it must always be remembered, however, that each component may be subject to recycling phenomena, and what is used may be the result of several processes. Indeed, it usually is. Examples are numerous. They have evolved in complexity and comprehensiveness from the early days of fallout to the massive compilations produced by the Lawrence Livermore Laboratory, Oak Ridge, and others, to be discussed in the next section.

E. Some Landmark Modeling

1. Lawrence Livermore Laboratory

Since the Biomedical Research Division of the Lawrence Livermore Laboratory (at that time Lawrence Radiation Laboratory) was developed with a charge to enter comprehensive studies of environmental contamination due to fallout, much of their earlier efforts went into modeling.

There was a series of laboratory reports that estimated the maximum contamination of agricultural land from fallout (Tamplin 1967), the maximum dose from internal emitters (Ng and Thompson 1966), biological guidelines for device design^(a) (Burton and Pratt 1968), a large handbook for estimating the maximum internal doses from radionuclides released to the biosphere (Ng et al. 1968),^(b) and estimation of the maximum dose from internal emitters in aquatic food supply (Tamplin, Fisher, and Chapman 1968).^(c) All of these used the format of developing both preshot prediction and means for postshot evaluation and were comprehensive. No radionuclide was dismissed as unimportant unless and until a critical analysis proved it to be. This meant running through all of the radionuclides produced and all of the potential pathways. Postshot predictions

(a) The biological guidelines for device design involved amounts of material, particle fluxes, choice of the least hazardous of several possible design materials under worst possible case assumptions, which cross sections might be important, etc. This was an unusual crossover of biological scientists into details of device design, but the Lawrence Radiation Laboratory has routinely made a point of ignoring the lines between disciplines. The idea of designing a device around minimal biological hazards was, of course, part of the Plowshare philosophy (chapter 14).

(b) This was a document full of tables and utilized the "unit-rad deposition" concept, the minimum deposition of each isotope in $\mu\text{Ci}/\text{m}^2$ that could result in a thirty-year internal dose of 1 rad to the organ or tissue under consideration. Other tables ranged from metabolic data derived from Standard Man (Reference Man—chapter 16) and the uptake and distribution in organs to fraction of intake secreted in milk, ratios of aquatic diet to terrestrial diet, concentrations in terrestrial foodstuffs, seawater foodstuffs, and freshwater foodstuffs. The unit-rad deposition was calculated for both the forage-cow-milk pathway and the soil-root pathway.

(c) For this one they chose, for illustration, the thirty-year dose to infant's bone from an event such as the construction of a sea-level canal with nuclear explosives.

had to be reliable with no "surprises" at short or long times or great distances.^(a) Thus, both preshot predictions and postshot documentation were extended to distances of two thousand to three thousand miles from the point of detonation.

Obviously, this enterprise was closely related to the pathway and dosimetry analysis carried out slightly later at Oak Ridge in connection with Project Plowshare, especially around the potential for construction of a sea-level canal in Panama or Colombia described in chapter 14.

Some years later, a sixth part to this classic compendium appeared. It concerned the transport of nuclear debris by surface and ground water (Fisher 1972).

2. Modeling at Oak Ridge

In addition to the modeling and pathway analysis aimed specifically at possible use of nuclear explosives, described in some detail in chapter 14, the Oak Ridge environmental sciences people extended their modeling to more general situations. It was built upon the Livermore work on assessment, especially that in UCRL-50163. The product was a "cumulative exposure index" (CUEX) for assessing environmental releases of radioactivity (Kaye et al. 1971). It utilized the EXREM and INREM computer codes for dosimetry described in chapter 14, an atmospheric dispersion model called AIRMOD, a terrestrial transport model called TERMOD, and it could apply to single exposure or multiple exposure modes and to many radionuclides and several pathways. The authors consider CUEX as a more thorough and realistic system than the maximum permissible concentration (MPC) because all modes of exposure are included, not just an MPC for air or for water. Also, the MPCs are basically derived from models used for occupational exposure with a scaling factor to the general population.

The CUEX methodology was tested against actual monitoring data from several sites (Parzyck, Witherspoon, and Till 1976). These were Haddam Neck pressurized water reactor (a boiling water reactor), the CP-5 reactor at Argonne National Laboratory (tritium), and ¹³¹I and gross alpha concentrations in the vicinity of Oak Ridge National Laboratory (ORNL). The estimated concentrations and doses were usually within a factor of two of the measured values.

The developers of CUEX indicate that it would need to be calculated for each type of release at each site. "It is not envisaged for general application to all or most situations as the ICRP's Maximum Permissible Concentrations . . . are applied (somewhat erroneously)" (Kaye et al. 1971, pp. 7-8).

A related model called CUMEX (cumulative hazard index), in contrast to CUEX (cumulative exposure index), was developed by the same group and applied to nonnuclear hazards, such as cadmium (Walsh, Killough, and Rohwer 1978).

Both the Lawrence Livermore and Oak Ridge efforts represent something of a zenith of pathway and dosimetric analysis. They put to shame the relatively superficial efforts and approaches applied at the time in the field of environmental contamination by chemically toxic substances, with the possible exception of cadmium. Only now are comparable enterprises appearing on that front.

3. Reactors and other Nuclear Facilities

Some of the earliest efforts at modeling concentrated on analysis of the hazards of environmental contamination from nuclear facilities. At the first Atoms for

(a) They were determined there would be no instances like the iodine-in-milk situation that occurred in Utah (chapter 12).

Peace Conference in 1955, Parker gave a condensed overview of the types of potential hazards from various types of reactors, from chemical processing plants, etc. This included details of atmospheric dispersion work done at Hanford (Parker 1956). Parker and Healy (1956) described the environmental effects of a major reactor disaster, including health effects and estimates of property damage. Both required some basic modeling work. Details of the calculations were given by Healy (1957) in a Hanford report.

In the ensuing years, many and increasingly sophisticated analyses took place. At the second Atoms for Peace Conference, Leonard (1958), from Convair-Fort Worth, used predictive methods for assessment of hazards associated with fission product release. Many others appeared over the years. Some have been referenced in earlier chapters.

A landmark effort occurred in preparation of the Reactor Safety Study carried out by AEC but released by the Nuclear Regulatory Commission in 1975 (NRC 1975). There were external and internal dosimetry models and a chronic exposure model that considered the behavior of radionuclides in soils, the plant-root-milk pathway, and differential equations for a compartment model. Other major reports from the U.S. government were those on the nuclear fuel cycle, the liquid metal fast breeder reactor, etc. In a sense, every environmental impact statement of recent vintage contains elements of one or more of these models.

F. Specifics Regarding a Few Pathways

We could not help but introduce some details regarding specific nuclides in specific pathways while discussing other major topics in these chapters on the environment. Yet, there are areas of research and of scholarly reporting and analysis that we have not reviewed. A few of these form the substance of this section.

1. Strontium Isotopes

In chapters 12 and 13, we discussed the relationship of strontium to calcium, discrimination for calcium and against strontium in the biosphere, and the reasons for considering its two significant isotopes, ^{89}Sr and ^{90}Sr , as "critical radionuclides." We looked briefly at its appearance in the transfer through foods, especially milk, and its effects in animals. We remarked on the contributions its study had made to understanding the biochemistry of bone. Is there anything left to discuss? Of course there is.

First, let us look at pathways for radioactive strontium other than milk. In Russell's (1966) classic early volume called *Radioactivity and Human Diet*, Comar (1966) remarks that deposition of strontium in meat and eggs makes a small contribution compared to milk because these provide only a small portion of dietary calcium. There seems to be little or no discrimination between strontium and calcium between the circulating fluids and soft tissues, or the components of eggs.

Perhaps the most comprehensive and consistent review of transfer factors for various radionuclides began with the 1962 edition of the UNSCEAR (United Nations) reports already cited. Each new edition brought summaries of work done all over the world. In a 1980 document, we find an equation for evaluation of the transfer factor for ^{90}Sr in each individual component of the diet. The quantities are expressed as they appear in the UNSCEAR document:

The transfer from deposition to diet is quantitatively described by means of the transfer factor P_{23} , defined as the time-integrated $^{90}\text{Sr}/\text{Ca}$ quotient in the diet divided by the ^{90}Sr integrated deposition density. The integrals may be replaced by summations if the relevant quantities are assessed over discrete intervals of time. In fact, annual values are the most generally available information. The transfer factor P_{23} is usually expressed in mBq y/gCa per Bq m^{-2} .

The transfer factor may also be evaluated for each individual component j of the diet p_{23}^j . Expressing the fractional contribution of component j of the diet to the total dietary calcium intake as W_j , the transfer factor for total diet is

$$P_{23} = \sum W_j p_{23}^j$$

The transfer to diet from a specific deposition occurs over an extended period as long as ^{90}Sr remains in soil available for root uptake. Several models have been used to predict the ^{90}Sr levels in diet from data on past deposition densities. The model which appears at present to be most adequate for expressing the transfer of ^{90}Sr from deposition to diet is

$$C(n) = b_1 f(n) + b_2 f(n-1) + b_3 \sum_{m=1}^{\infty} f(n-m) e^{-\mu m}$$

where $C(n)$ is the $^{90}\text{Sr}/\text{Ca}$ quotient in total diet, in a food group, or in an individual food item, in the year n ; $f(n)$ is the annual deposition density in the year n , and b_1 , b_2 , b_3 , and μ are factors which can be derived from reported data by regression analysis. The factor b_1 represents the contribution to dietary ^{90}Sr per unit deposition density in the current year, while the factor b_2 expresses separately the contribution in the previous year, reflecting also the use in the current year of stored food produced in the previous year. The sum in the third term expresses the contribution to dietary ^{90}Sr from the deposition density in all previous years, resulting from root uptake and taking into account decay and loss of availability due to downward movement in soil or to other physical or chemical changes which may occur. The inverse of μ is the mean life of available ^{90}Sr in soil, which varies for individual foods and soil conditions.

The transfer factors for individual food types are in reasonable agreement for milk products in all three areas, and for vegetables, fruit, and grain products, in New York and Denmark. Differences are due to different definition of food groups and also different soil conditions and agricultural practices in the three countries. The parameters for the Argentine diet are probably more uncertain, mainly because the deposition density rate did not peak as sharply in the southern hemisphere, resulting in a decreased discrimination power of the regression analysis.

The contribution from each food group to total dietary calcium intakes, W_j , vary from country to country due to different consumption habits. To compare relative contributions to the total diet transfer factor P_{23} , it is necessary to compare the product $W_j p_{23}^j$. In New York the contribution to total dietary $^{90}\text{Sr}/\text{Ca}$ quotients is approximately equal from three food groups: vegetables 28%, milk products 27% and fruit 26%. In Denmark the greatest contributors are grain products 46%, milk products 28% and vegetables 18%. Meat is a minor contributor in both countries. In Argentina the contributions are grain products 39%, milk products 38%, fruit and all vegetables 13%, and meat 10%. (UNSCEAR 1980)

The parameters found for New York, Denmark, and Argentina are shown in table 15.5.

This may be more than many readers wish to know about transfer factors for a given element, but it shows what can be done from the research efforts mounted over many years.

TABLE 15.5. Parameters of the Transfer Function for ^{90}Sr Between Deposition Density and Diet (regression fits through 1976 data from New York, Denmark, and Argentina). [See text for definition of terms.]

Parameter a/	Milk Products	Vegetables b/	Fruits c/	Grain Products	Meat Fish Eggs d/	Total Diet
— New York —						
b_1	0.69	0.96	1.37	0.88	0.003	0.91
b_2	0.23	0.38	0	1.88	0.22	0.58
b_3	0.19	1.03	0.90	0.30	0.26	0.33
μ	0.13	0.07	0.03	0.13	0.24	0.09
P_{23}^j	2.27	15.54	31.00	4.92	1.16	5.03
W_j	0.582	0.089	0.039	0.179	0.111	1.0
$W_j P_{23}^j$	1.32	1.38	1.21	0.88	0.13	5.03
	-----	-----	4.92	-----	-----	5.03
— Denmark —						
b_1	0.99	2.61	10.06	0.87	1.86	1.07
b_2	0.46	0	0.45	2.48	0.37	1.23
b_3	0.23	0.88	0.45	0.03	0.32	0.17
μ	0.13	0.06	0.02	0.02	0.15	0.08
P_{23}^j	3.08	16.92	32.89	4.65	4.18	4.38
W_j	0.44	0.05	0.01	0.48	0.02	1.0
$W_j P_{23}^j$	1.36	0.85	0.33	2.23	0.08	4.38
	-----	-----	4.85	-----	-----	4.38
— Argentina —						
b_1	1.21	1.41	0.16	6.65	1.56	2.32
b_2	1.09	0.90	0	6.38	1.81	1.25
b_3	0.21	0.18	0.38	0.26	0.07	0.12
μ	0.19	0.13	0.26	0.04	0.02	0.09
P_{23}^j	3.29	3.59	1.45	19.39	6.82	4.87
W_j	0.571	0.129	0.129	0.10	0.071	1.0
$W_j P_{23}^j$	1.88	0.46	0.19	1.94	0.48	4.87
	-----	-----	4.95	-----	-----	4.87

a/ The unit for parameters b_1 , b_2 , b_3 is mBq y (gCa)^{-1} per Bq m^{-2} . The unit for parameter μ is y^{-1} . The unit for the transfer factor P_{23} is mBq y (gCa)^{-1} per Bq m^{-2} . W_j is the fractional contribution of component j to the total Ca in diet.

b/ Values given in this column for Argentina include fruits and vegetables.

c/ Values given in this column for Argentina are for root vegetables.

d/ Values given in this column for Argentina are for miscellaneous food.

Source: Modified slightly and reset from UNSCEAR 1980.

An area of indirect but important bearing on biomedical problems is the effect of soil chemistry on the movement and complexing of strontium. A large amount of work has been done in this area, much of it in the USSR and much of it in the 1950s. The field involved scientists from many laboratories and included some of the experimental work described in chapter 13. Nevertheless, much of it did not involve the internal emitter establishment as described in this book. C. W. Francis (1978), a member of the Environmental Sciences Division at ORNL, has produced a comprehensive and critical review of the movement of radio-strontium in soils and its uptake by plants. It includes as much as possible of the Russian work, which appears to be responsible for well over half of the

research findings described. An overview of the subjects covered can be gleaned from a list of the chapter headings.

1. Distribution of Fallout Strontium-90 in Soil Profiles
2. Movement of Radiostrontium in Soils
3. Strontium Soil Reaction Products
4. Plant Uptake of Strontium from Nutrient Solutions
5. Strontium Uptake by Plants as Influenced by Soil Properties
6. Soil Amendments Affecting Radiostrontium Uptake by Plants

The research leaves little doubt that, while strontium is not strongly complexed to soil constituents, differences in soil chemistry can, as expected, greatly influence its availability for transfer and its uptake by plants. Quite surprising was the fact that liming, i.e., addition of calcium, was useful in reducing the uptake of strontium by plants only when they were growing on acid-base-unsaturated soils. With pH above 6.2 and base saturation above 75%, liming was not a practical method for reducing strontium uptake. The largest effect was seen with the addition of phosphorus, and this was most effective with tropical-type soils or neutral or alkaline soils. Work in both the United States and the USSR showed that applications of large amounts of phosphate fertilizer, plus liming, did, indeed, reduce radiostrontium uptake from contaminated soils. Unfortunately, the quantities required exceeded twenty metric tons per hectare, not economically feasible except under exceptional conditions.

2. Cesium

a. General

Movement of cesium isotopes in the environment was studied zealously, and in depth, from the beginning of the contamination episodes, especially fallout from weapons tests. We saw earlier (chapter 13) that cesium is bound tightly to many components of soil and that this can influence uptake into biota.^(a) Yet, as we saw in chapter 12, cesium isotopes are fairly homogeneously distributed in organisms. It follows potassium in its metabolism and accumulates in soft tissues, very little in bone in contrast to strontium. In nuclear fission, the radioisotopes of cesium are of considerable importance since they appear in high yield, and the most important isotope, ¹³⁷Cs, has a moderately long radioactive half-life (30 yr). By contrast, it has a relatively short biological half-life, 74 to 180 days in different organisms.^(b) There can be much turnover and recycling of cesium in the environment and in biota. Thus, the environmental transfer phenomena for cesium are quite different from those for strontium.

Since cesium has a short biological half-life in contrast to the long retention in bone of strontium isotopes, there was no equivalent of the "Sunshine Project" for cesium and, in a sense, it was eclipsed in the early work by strontium. Yet most of the same laboratories and workers were involved in the investigation of cesium as we met earlier for strontium. When it was apparent that the sources of radiocesium were continuously renewed during the era of atmospheric testing, the level of work grew apace. Indeed, some of the highest doses to humans from global fallout have occurred from cesium in the arctic

(a) For additional evidence, see Cummings et al. (1969) in work at the Southeastern Radiological Health Laboratory.

(b) National Academy of Sciences-National Research Council report to Federal Radiation Council, December 1964, cited in chapter 12. Children can be less by factors of three.

food chain (see below). There was also ample evidence of recycling of cesium in areas contaminated by radioactive waste.

Transfer of cesium to the diet is normally quite high for the first few years after deposit. It becomes low if the source has dwindled to largely the complexes in soil. However, in many situations this does not occur. Wallace, Romney, and Wood (1971), from the University of California, Los Angeles (UCLA), studied stable cesium circulation in the desert ecosystems of NTS. They found that, while the rates were low, circulation was definitely occurring and continuing. The compartments studied were soil, several plant species, arthropods, reptiles, and mammals. There was a progressive narrowing of the potassium/cesium ratio from plants to reptiles to mammals.

In other work from UCLA, Romney et al. (1971) investigated areas of "old" fallout over a period of several years. Transfer from abiotic to biotic components of the environment was continuing from shots in 1953, 1955, and 1957 to the latest time of study (about 1966–1970 for this publication). There was a decrease in the role of the inhalation route as the amounts of radioactivity available for resuspension by wind gradually fell, but ^{137}Cs continued to move through the gastrointestinal tract of jack rabbits and kangaroo rats. The amounts were not large, but sufficient to indicate continual recycling of the nuclide.

Perhaps the longest study period, thirty years, involved the White Oak-Lake flood plain at Oak Ridge. Dahlman and Van Voris (1976) went back over an area contaminated since 1944. Practically all of the ^{137}Cs soil was still within 60 cm of the surface. Relative concentrations were 0.6 for root/soil, 0.03 for above-ground vegetation/soil, and 0.04 for above-ground vegetation/roots. Furthermore, the distribution between plants and soil was the same at the time of this study as it was fifteen years earlier in 1959, i.e. about 0.03. This may be one of the most steady steady-states in radioecology.

As we have already seen, much work was done to ascertain the movement of cesium in food chains. While there is an ample amount in milk, grain products and meat provide about half of the ^{137}Cs intake (UNSCEAR 1972, p. 52), and the amount in milk is strongly dependent on deposition rates.

In general, the researches on cesium have not indicated the consistent discrimination at each step in the transfer process that we saw for strontium (chapters 12 and 13). Yet, workers at the University of Utah studied the cesium/potassium ratio in many animal species and found that it was two to three times higher in the organism than in their normal diets (Pendleton et al. 1965). It was a function of the potassium intake and of age. Thus, there was some concentration with trophic level increases.

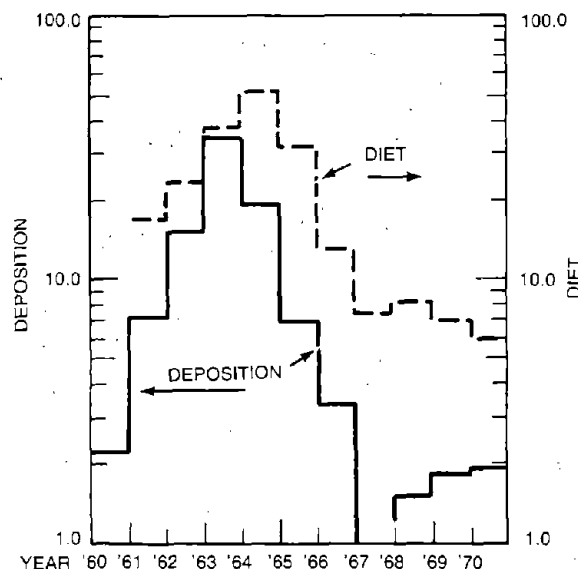
Other research bearing on ascertaining transfer factors included the many studies on ^{137}Cs body burdens in humans measured by whole-body counting. In addition to the several studies quoted in earlier connections, a PHS survey of children in Florida and Illinois, done in 1969, should be added (Karches et al. 1969), as well as later research in Utah correlating ^{137}Cs body burden with milk content (Lloyd et al. 1973). The latter work went back to the nineteen dairy farms utilized in the 1962 to 1966 fallout studies (chapter 12) and the testing of a model. They conclude that prospective or retrospective projection of human cesium body burdens may be made from estimates of milk content.

An interesting set of studies on radionuclides in the diet of adults in Chicago was carried on by Gustafson at Argonne National Laboratory (ANL). It resulted in several reports, examples of which we have already seen in other connections. In 1970, Gustafson showed how the content of ^{137}Cs in the diet could lag

the deposition. The maximum in diet occurred about a year later than the maximum in deposition. The amount in diet held up even though deposition decreased markedly. This could be presumed to reflect the recycling phenomena we have discussed.

A sample of the data is shown as figure 15.9.(a)

FIGURE 15.9. Annual average ^{137}Cs deposition in the midwestern United States, and annual average ^{137}Cs level in the Chicago adult diet. (Redrawn from Gustafson et al. via NCRP 1977. [The ordinate units for deposition are mCi/km^2 , for diet pCi/gK .] Reprinted with permission of the National Council on Radiation Protection and Measurements, Bethesda, Maryland, copyright 1977.)



The facts above and recent events such as the Chernobyl reactor accident (chapter 21) suggest that we should probably have designated cesium as a "critical" radionuclide, along with strontium, in considering fallout. The short biological half-life led the thinking astray, since the phenomena of recycling were not factored in for the early computation. We are still learning!

b. Cesium in the Arctic and Subarctic—A Special Case

In earlier connections, we have described briefly the fact that the very short food chain of lichen-caribou (or reindeer)-man in arctic and subarctic environments changed the relationships characteristic of temperate climates. Details are well traced in the book by Whicker and Schultz already cited (vol. 1, p. 173 et seq.). It appears that one of the earliest clues came from work of a Professor Lidén at Lund, Sweden, who found significantly higher body burdens of ^{137}Cs in Scandinavians who had eaten significant quantities of reindeer meat than in others (Lidén 1961). This was in 1960–1961. Two reindeer-raising Laplanders had as much as thirty to forty-five times as much ^{137}Cs as individuals from Lund. In 1962, Hanson, from Hanford, found ^{137}Cs burdens in Alaskan Eskimos comparable to those in the Laplanders. By the time of the Stockholm symposium on radioecological concentration processes, the subject was under intensive study in Alaska (Hanson, Watson, and Perkins 1967), in Sweden (Lidén and Gustafsson 1967), in the USSR (Nevstrueva et al. 1967), in Finland (Miettinen 1969a,b), and in Norway (Hvinden and Lillegraven 1961).

(a) This is from the work of Gustafson at ANL, but taken from a summary report on cesium from the environment to man prepared by Scientific Committee-23 of the NCRP (NCRP 1977). This report provides a succinct summary on environmental ^{137}Cs , with particular emphasis on dosimetry.

Even though the populations were relatively small, a significant number of individuals were studied. Some Alaskan Eskimos reached, and even maintained, body contents that delivered from three to four times the annual radiation dose attributed to natural background, taken as 150 mrad. This was much more than normal population standards would permit. Since the doses were the result of nuclear weapons testing, and there was talk of Plowshare events in Alaska, intensive efforts from U.S. laboratories^(a) went into studying the subject (see also chapter 12).

The Hanford group worked on the North Slope in Alaska (Hanson 1967), a group from Canada looked at subarctic Canada (Bird et al. 1965), and the Miettinen group from Finland looked further at Finnish Laplanders (Miettinen and Häsänen 1967). Like the Hanford group in Alaska, the Finns toted whole-body counters to remote villages (their use was possible because of the relative ease of measuring ^{137}Cs), and they measured both the populations (Miettinen 1969b) and the flora (lichens) and fauna (caribou and reindeer). They also sometimes brought the people to the laboratories for measurement.

This international effort showed consistently that the cesium in Alaskan Eskimos and Finnish Laplanders and other inhabitants of the subarctic was as much as a factor of one hundred above that in people in the north temperate latitudes. Other radionuclides, including "natural elements" such as ^{210}Pb and ^{210}Po , behaved in the same manner as was found by Persson (1967) from Sweden and by the Finns (Kauranen and Miettinen 1967). Indeed, ^{210}Po also reached quite high levels (see chapter 4).

The difference lies, of course, in two peculiarities of transfer factors in the arctic and subarctic environment: (1) lichens cover a large part of the surface area, and their surface structure holds any deposited radionuclide tenaciously (half-life as high as seven hundred days, even ten years); also lichens are very long-lived; and (2) the diet of a typical Lapp may average 70% to 90% reindeer or caribou meat. That meat had received ^{137}Cs in a mobile form directly from the lichens. There was little interposition of soil-forage-milk pathways and the like. There were, of course, seasonal variations because of seasonal changes in diet.

In retrospect, it may seem that an inordinate amount of effort went into this work. The reasons and the mechanisms seem fairly obvious and not at all surprising. However, we must remember that this was during the peak of the fall-out polemics. There were U.S. citizens and world citizens carrying body burdens above those considered allowable by the current recommendations of the Federal Radiation Council for individuals in the population or for populations (1,000 nCi).^(b) The testing was still under way at the beginning of the work. How much higher would these levels go? Was this a prologue to further increases in temperate latitudes? There was much concern, some of it conscientious and justified; some of it unwarranted, since the fact that this was a very unusual food chain with unusually high transfer factors was forgotten or lost sight of.

(a) A large portion of the published work from the United States for the earlier years came from Hanford. They actually began in 1959. In later years, the Lawrence Livermore group began a somewhat more wide-ranging survey that encompassed many isotopes in addition to ^{137}Cs . However, the Arctic story is primarily a cesium story. A listing of some of the Hanford and UCRL reports on this subject is given as note 2 at the end of this chapter.

(b) Amounts measured were not greatly higher, e.g., 1,280 nCi; 1,620 nCi; 3,000 nCi; etc.

It can be concluded without doubt, however, that short food chains with high transfer factors can be dangerous and perhaps produce unexpected surprises. These phenomena in the Arctic strengthen further the conclusion that cesium should have been designated as a critical "radionuclide."

3. Iodine

a. General

In earlier chapters, we considered the development of ideas concerning iodine releases from nuclear reactors and from chemical processing plants, and the large enterprise that surrounded iodine in fallout. We saw that it was iodine in the environment that probably first focused attention on the importance of food contamination from fallout. We reviewed in some detail the work done in Utah and Nevada regarding milk contamination from the Nevada tests and the generalized milk networks set up around global fallout. We also traced the gradual shift in emphasis from thinking of iodine as primarily an inhalation hazard in occupational exposure or local releases to primary concern about its presence in milk and dairy products. Yet, there are some aspects of iodine transfer in the environment that need to be considered further before we can close the discussion. These aspects will be reviewed briefly in this section.

Appropriate to the fact that much of the work on iodine in the environment began at Hanford is the fact that Hanson wrote a succinct review on iodine for the First National Symposium on Radioecology, described in chapter 11 (Hanson 1963). This review included both stable and radioiodine in many media, the utilization of iodine by plants and animals; and the basis for transfer factors that could be used in later models. At the same symposium, French and Larson, from UCLA, discussed environmental pathways for iodine from nuclear tests in arid regions (French and Larson 1963). These and many others made it quite clear that the chemistry of iodine in reactors, in released clouds, and in the environment can be quite complex, but that surface adsorption can play a prominent role at the forage step. Evidence for a predominant role of ingestion came from two facts: (1) animals existing in a contaminated environment, but prevented from ingesting contaminated material, showed little or no radioiodine in their thyroids; and (2) thyroid radioiodine continues to increase for several days after a contaminating event, a course not expected after inhalation, but consistent with continuing ingestion.

Soldat (1963, 1965) added to insight into the passage of ^{131}I in food chains by measuring the kinetics of its behavior in various media, including air, pasture, milk, and cattle thyroids. The work was reported at the Hanford life sciences symposium on the biology of radioiodine in 1963. An average delay of about six days occurred between the peak in vegetation and appearance in milk, about twelve days between peak concentration in grass and in the cow's thyroid. (The British developed slightly shorter times from their investigations around Windscale.) Average ratios of several components needed to estimate transfer functions were developed:

$$\begin{array}{lll} \frac{\text{pc/kg of grass}}{\text{pc/m}^3 \text{ of air}} \approx 4,200 & \frac{\text{pc/g thyroid}}{\text{pc/kg grass}} \approx 0.45 & \frac{\text{pc/l milk}}{\text{pc/m}^3 \text{ air}} \approx 600 \\ \frac{\text{pc/l of milk}}{\text{pc/kg grass}} \approx 0.15 & \frac{\text{pc/g thyroid}}{\text{pc/l milk}} \approx 3.0 & \end{array}$$

Soldat also gave the ratio of doses to the thyroid from milk compared to air—20 for a 20-g thyroid and 400 for a 2-g thyroid.

The UNSCEAR 1972 report has much to say about the complexity and variability of the behavior of iodine in the environment. The amount of activity in the form of particles can vary from 10% to 90%, with the balance in gaseous form. Doses can be calculated only if *local* deposit and transfer patterns are known or if milk levels (fresh milk is the principal source among the foods) are known. Also, neither field nor laboratory techniques for measuring iodine separate from gross beta activity were available in the years of most feverish activity in measuring and characterizing fallout. Thus, for 1952, 1953, and 1957, integrated milk levels were derived from beta activities in air, as we saw in chapter 12.

As techniques advanced, specific models for iodine isotopes gradually emerged. A major development began in the 1960s at Idaho Falls that had a strong influence on these and on the allowable limits for iodine in the environment. We will review this in the next section.

b. The Controlled Environmental Radioiodine Tests at Idaho Falls^(a)

In chapter 14, we reviewed field exposures of animals to fission products from melted reactor fuel elements at the National Reactor Testing Station in Idaho. Iodine predominated in the releases from “green” fuel elements in these tests (called FPFRT for Fission Product Field Release Tests). At the time, we remarked that further special tests took place at Idaho Falls, but they were so intimately related to the analysis of transfer factors in the environment that we would postpone discussion to chapter 15. These were the Controlled Environmental Radioiodine Tests (CERT), whose stated objectives were:

1. to derive a mathematical model to predict the deposition and retention of radioiodine as a function of (a) vegetation type and state, (b) chemical and physical form of radioiodine, and (c) meteorological conditions
2. to derive a mathematical model to predict the transfer of radioiodine from vegetation to milk
3. to derive a mathematical model to predict the dose from radioiodine to humans.

It was determined that a very important transfer factor to be characterized was the “deposition velocity” (V_g) for ^{131}I from air to pasture grasses or vegetation. To assess it and other relationships for the air-vegetation-cow-milk-human food web, the Idaho Falls group decided to set up a series of tests with ^{131}I generators and a sample grid in areas of typical pasture grass. There were also some cows, kept in an experimental dairy farm, which could be fed the grass and even some human volunteers who placed themselves in the passing cloud of iodine vapor, or who drank milk from the cows and had their thyroid glands counted at the laboratory.

The first report (Hawley et al. 1964) was labeled “preliminary” but seems to have been quite complete. A total of 970 mCi of ^{131}I were released as a gas over a thirty-minute period onto a pasture of crested Wheatgrass. About 13% of the iodine deposited on the sampling grid and 1.5% on the grass. Deposition

(a) The author is greatly indebted to Dr. Eddie W. Chew, Chief Environmental Sciences Branch, Radiological and Environmental Sciences Laboratory, Idaho Operations Office, DOE, for copies of the pertinent IDO reports.

velocities were calculated as 0.4 to 0.8 cm/sec with an average of 0.6 cm/sec. Effective half-life on the grass was about 3.5 days, and the ratio of activity in milk (pCi/l) to that on the grass (pCi/g) was 240 ± 35 .^(a) The average human thyroid uptake of the ingested ^{131}I was 19% and the predicted dose to the thyroid 0.39 rad. It was a satisfactory test.

No further reports appeared for nearly two years. However, the tests continued in the interim, viz., September 1964, December 1964, May 1965, and June 1965. The schedule included two tests over open-range-type vegetation, two tests over irrigated pastures, and one over snow-covered ground. Meteorological conditions varied from lapse conditions (two tests), to inversion conditions (two tests), and neutral conditions (one test).

A report edited by Hawley (1966) gives progress through 1965 and summarizes the first five experiments. A sixth test, using methyl iodide, and a seventh designed to provide information on movement under late fall and early winter conditions were described in a report edited by Bunch (1966). A later report by Bunch (1968) gives a summary of the purposes of each test, the location of the release, etc. A copy of this summary of nineteen tests is given as table 15.6.

As time wore on, the cows and human thyroid steps were sometimes omitted to allow concentration on some of the more difficult steps at the front end of the chain. Mathematical models for bovine metabolism of ^{131}I ^(b) and other steps began to emerge, and these were compared to other models, such as that proposed by Garner (1967).

Further information was contained in a report by Zimbrick and Voillequé (1969) and in a paper presented by Pelletier and Zimbrick (1970) at the Health Physics Society Mid-Year Topical Symposium in Augusta, Georgia.

Along with the field work, it was found necessary to develop a laboratory experimental program (late in 1964) with objectives to isolate each variable more than could be done in the field, and to improve techniques. This program was dubbed "CERTLE."

Principal results as outlined in 1967, but actually not changed much in subsequent work, included the following:

1. No significant difference was observed in behavior of molecular iodine from a few hundred meters out to two miles from the release point.
2. Deposition velocity figures were usually below 1 cm/sec but varied with areal grass density.
3. A strong linear relationship existed between normalized deposition velocity and friction velocity under moderate wind speeds in an unstable atmosphere. It was not so strong with light winds and a stable atmosphere.
4. Deposition velocity for methyl iodide is on the order of 0.05% of that of molecular iodine.
5. The average uptake fraction in human thyroid from contaminated milk was 0.19.
6. The average uptake fraction in human thyroid by inhalation was 0.30 (three subjects, one release).
7. A reasonably satisfactory model for bovine metabolism of radioiodine was constructed.

(a) The units for this ratio are pCi/l of milk to pCi/g of grass, whereas those on page 1298 use pCi/kg grass. The ratios in common terms would be 0.16 versus 0.24 or 150 versus 240, depending on the units chosen and if the agreement between the studies is satisfactory.

(b) Interestingly, this included a compartment for radioiodine in body fluid not available for secretion in milk.

TABLE 15.6. Objectives of Specific CERT Tests

Test Number	Release Time	Date	Location	Test Objectives
1	1500	5/27/63	Atomic City Area	To check techniques and experimental design to be used in establishing three basic relationships under known natural release conditions: (1) The amount of radioiodine in the air relative to that in soil and vegetation. (2) The amount of radioiodine on the vegetation relative to that in milk. (3) The quantity of radioiodine in milk relative to that in the human thyroid after drinking the milk.
2	1344	9/2/64	Experimental Dairy Farm (EDF)	To determine the three relationships in Test 1 above using an irrigated pasture typical of present farming practices in this area.
3	1354	12/11/64	EDF	To obtain information on the meteorological aspects of iodine deposition using snow as the surface for deposition.
4	0430	5/27/65	South of SL-1	To measure the deposition velocity of I_2 on grass during stable atmospheric conditions.
5	0515	6/10/65	South of SL-1	Same as Test 4.
6	1400	9/14/65	ICPP Stack (Idaho Chemical Processing Plant)	To evaluate the behavior of CH_3I in the milk-food chain.
7	1410	11/22/65	EDF	To determine radioiodine behavior in late fall or winter.
8	2040	5/31/66	NE of ICPP	To check techniques and experimental design to be used in evaluating the deposition of radioiodine under various meteorological conditions.
9	0245	6/7/66	NE of ICPP	Same as Test 8.
10	1040	6/14/66	Test Grid 3	To determine the behavior of elemental iodine over travel distances typical of postulated reactor accidents.
11	1323, 1331	7/21/66	EDF	To evaluate the behavior of CH_3I in the milk-food chain.
12	2108	7/26/66	EDF	To measure the deposition of CH_3I at night.
13	1020	8/3/66	EDF	To measure the deposition of elemental iodine as a function of meteorological conditions.
14	0234	8/5/66	EDF	Same as Test 13.
15	0540	8/5/66	EDF	Same as Test 13.
16	0230	8/24/66	EDF	Same as Test 13.
17	0530	8/24/66	EDF	Same as Test 13.
18	1955	9/8/66	EDF	Same as Test 13.
19	1024	11/7/66	EDF	To evaluate the behavior of radioiodine in late fall.

Source: Reset from Bunch 1968.

In addition to the iodine tests, the Idaho Falls group did work with ^{137}Cs on a Michigan dairy farm (referenced in chapter 12), onsite at the National Reactor Testing Station, and more general radioecology and ecology programs.^(a) The significance and uses made of some of this work will become apparent in the next section.

c. The Factors of 700 and 1,000

In the work of Soldat' (1963) described above, we saw a factor of 600 between pCi/l of milk and pCi/m^3 of air. This, and similar figures from other sources (e.g., the fallout studies in Utah and other work on the iodine-milk pathway), led the regulators to considerable concern about the validity of the then-current maximum permissible air concentration $[(\text{MPC})_a]$ of iodine for population exposure. Table II, Appendix B of Title 20 of the Code of Federal Regulations (10 CFR 20) had set a "legal" $(\text{MPC})_a$ in the environment for ^{131}I of $1 \times 10^{-10} \mu\text{Ci/cc}$. The fact that such values did not take any account of the "reconcentrations"^(b) and food-cycling phenomena we have been examining disturbed the regulators. They had already urged that all releases be "As Low as Reasonably Achievable," but this did not seem to be enough.

In a new appendix (Appendix I)^(c) to Part 50 of the Code of Federal Regulations, which covered licensing of production and utilization facilities, some numbers were attached to the "As Low as Reasonably Achievable" recommendations. These were designated to apply specifically to the effluents from light-water-cooled reactors. This placed a limit on annual total body exposure of individuals in unrestricted areas of 5 mrem and a calculated annual total radiation dose or dose commitment from all radioactive iodine and radioactive material in particulate form in effluents released to the atmosphere of 15 mrem to any organ from all pathways. These were a factor of one thousand lower than the extant occupational whole-body limit of 5 rem/yr and individual organ doses of 15 rem/yr, respectively, then in effect. It is commonly understood that this factor represented a rounding off, upward of a factor of seven hundred derived from the environmental transport work, much of it in the CERT tests. The exact calculations are not given in any official derivation, but they were common corridor conversation at environmental and regulatory meetings of the day and were fortunately summarized for posterity by Burnett (1970) at Oak Ridge.

The 10 CFR 20 table II Appendix B limit for ^{131}I in population exposure, i.e., $1 \times 10^{-10} \mu\text{Ci/cc}$, can be compared to an air concentration limit derived from use of a deposition rate of 1 cm/sec and other transfer factors in the milk pathway of $1.42 \times 10^{-13} \mu\text{Ci/cc}$. Conversely, we can take the Part 20 figure and divide it by the effective renewal constant and get an allowable concentration on vegetation of $0.625 \mu\text{Ci/m}^2$ if there were no environmental cycling. The figure with recycling using the numbers derived by the Federal Radiation Council (FRC 1964) (80 pCi per day and drinking 1 l of milk per day) was $8.9 \times 10^{-4} \mu\text{Ci/m}^2$. The ratio of these is about 700 in each case ($1 \times 10^{-10}/1.42 \times 10^{-13}$ and $0.625/8.9 \times 10^{-4}$). This ratio came from the iodine figures; it could have been derived in other ways also. If we add the smaller contribution of other radionuclides in the

(a) Bibliographies are available in Reports IDO-12078 (November 1973) and DOE/ID12098 (June 1983).

(b) The term is put in quotes since, while it is the one commonly used, it is not accurate. "Recycling" or simply cycling leading to increase in concentration is the process.

(c) Capital I, not the number one.

environment and the usual rounding off for safety, the factor of 1,000 is understandable. What is not so understandable is that this is still applied primarily to light-water-cooled reactors. They are not the only potential sources of iodine or other pollutants in the environment.

There were some later reassessments of the reduction factor for food chains, which were aimed especially at the deposition velocity figures. George (1970), who worked at the Sterling Forest (New York) Research Center of the Union Carbide Corporation, calculated that the thyroid dose for a six-month-old child by the direct inhalation pathway (at the ICRP limiting air concentration of 10^{-10} $\mu\text{Ci/cc}$) was 2.56 rem/yr. By contrast, the dose from the same air concentration and using 0.091 $\mu\text{Ci/l}$ per $\mu\text{Ci/m}^2$ as the milk-to-grass ratio and 1 cm/sec as the deposition velocity came out to 224 rem/yr. This was only a factor of 88 above the direct inhalation route. However, George does not object to the limits set in Appendix I. He cites the variability in some of the factors, e.g., the ratio of amount in milk to that in grass and in the deposition factor. Using different input values, he calculates a "reconcentration factor" of 200. Thus, use of the Appendix I dose limits may include a larger safety factor than stated above. George concludes, "The 700 factor is thus simply a number by which the $(\text{MPC})_a$ should be reduced when considering the milk exposure route."

Hoffman (1977), from Oak Ridge, contended that the environmental transport factor for air to pasture was underestimated in the earlier calculations because the measurements involved only the vegetation cut above a square meter of ground surface. This neglected the amounts deposited on detritus, root mats, and soil, while the calculation is for total deposit on a unit area of pasture. To account for this, he suggests use of two factors, V_g for total deposition velocity and V_D for vegetation only. He tabulates a large number of deposition velocities and other factors for the air-to-milk transport of ^{131}I and reviews the several assessment models done in various laboratories: Bayer (1972); Bryant (1964); Fletcher and Dotson (1971a); Hoffman (1973); Palms, Veluri, and Boone (1975); Soldat (1976); EPA (1973); AEC (1974a); and WASH-1400 (NRC 1975). The V_g values do indeed vary as seen in the CERT tests. The milk-to-air ratios resulting therefrom for ^{131}I varied from 190 to 5,400, with an average of 800.

Hoffman points out that the variations in milk-to-air ratios cannot be considered as errors. The physicochemical form of the iodine might have been truly different. The physicochemical form, including particle size, can move the available fraction of deposited radionuclide over a wide range, and we know this does vary. Indeed, he calculates a milk-to-air ratio for elemental iodine of approximately 6,000 (Ci/l per Ci/m^3) but points out that the value for small particle sizes may be only 300 or, for methyl iodide, only 30.

Hoffman,^(a) like George, does not suggest that the current standards should be changed, but urges more attention be paid in new work to the physicochemical form of the iodine in air so that future predictions can be made with fewer questions.

In 1978, another review appeared, also by Hoffman (Hoffman 1978), that concerned the values used for the transfer of iodine from diet to milk. His review led to recommendation of values slightly higher than those recommended in the NRC Regulatory Guide 1.109. The difference is again in the direction of more transfer than in the "legal" figures.

(a) A broad discussion of uncertainties in radiological assessment models can be seen in the chapter by Hoffman and Gardner (1983) in a book edited by Till and Meyer (1983).

Whether or not these modifications will lead to changes in regulatory position must await the publication of the revised Code of Federal Regulations. It is clear that, despite CERT and the variety of modeling work done, things are not yet cut and dried for the iodine-to-milk pathway.^(a)

4. Plutonium and the Transplutonic Elements, with Notes on Uranium and Thorium

We have seen (chapter 11) that plutonium is, in general, a markedly insoluble element.^(b) The other actinide elements, e.g., americium, curium and neptunium are somewhat more mobile, especially neptunium. Nevertheless, as a class, the actinides would not be expected to show transfer in the environment comparable to the other elements singled out for discussion above. Yet, there is a very large literature, and it is still growing, on transplutonic elements in the environment. We have already referred to the Gatlinburg symposium of the Nevada Applied Ecology Group (NAEG) (White and Dunaway 1977) and the IAEA symposium at San Francisco on transuranium nuclides in the environment (IAEA 1976). The Department of Energy got together several other symposia and sponsored the well-known and authoritative summary of environmental research on transuranium radionuclides edited by Hanson (1980). These are but a sample. Even more recent additions are a succinct summary by Watters (1981), given at the Snowbird symposium on actinides (Wrenn 1981a), and a short discussion by Kathren (1984) in his book on radioactivity in the environment. The locales for the work are largely the already familiar ones, PNL (Hanford), UCLA, the NAEG (chapter 14), Colorado State University, Lawrence Berkeley Laboratories, and the University of Utah and others for the more recent forays into environmental aspects of actinides.

Why should so much effort have been expended on a relatively insoluble group of elements? One obvious answer is the very long half-lives of many of these radionuclides. Another is their continuing presence in radioactive wastes. Another is the stimulus of the proposed "plutonium economy" associated with plans for a fast breeder reactor, a stimulus that has recently faded markedly in the United States, but is still important in other parts of the world. Another is the finding, described in earlier chapters, indicating that plutonium may be solubilized in the environment with time and become more mobile. And finally, there is the vaunted high toxicity^(c) of plutonium and general fear of the presence of

(a) We have had to neglect contributions from abroad, except for our earlier reference to Windscale. One is directly pertinent to the present discussion and should be noted. Heinemann and Vogt (1980), working at the Julich Nuclear Research Center in West Germany, measured deposition velocities of iodine in field experiments. The average deposition velocity was estimated at 2 cm/sec, somewhat higher than the figure used in U.S. calculations. Furthermore, they found that it was still greater on moist surfaces and, since there is more moisture in general at Julich than at Idaho Falls, they proposed using a factor of 3 cm/sec for the Federal Republic of Germany. On the other hand, they found deposition for aerosols to be lower by a factor of twenty and methyl iodide to be only 0.5% of that of elemental iodine.

(b) Concentration ratios in terrestrial systems are on the order of 10^{-3} to 10^{-6} but considerably higher in aquatic systems because of uptake by organisms like phytoplankton.

(c) Remember in chapter 8 we negated some of the claims that plutonium is "the most toxic element known to man."

even one atom of plutonium in the environment. In the presence of such fear, every laboratory bent over backwards to get all possible information.

This was not always so. In the early years, plutonium and the actinides were viewed as primarily inhalation hazards, and the venue was occupational rather than population exposures. This was strengthened by the demonstrations of high carcinogenic potential for plutonium in the lung (chapter 9). Indeed, even the early considerations of plutonium in fallout looked first at its potential as an inhalation hazard. This gradually changed as the environmental groups turned from fission products to plutonium and the other actinides. We find in the early seventies expressions of dismay that plutonium uptake and transfer in nature had been neglected in both aquatic environments (Noshkin 1972) and in terrestrial environments (Romney and Davis 1972) such as those around Hanford, Rocky Flats, NTS, the Trinity site, and others. It did, indeed, become apparent that the actinides moved through the environment, although the movement was slow and in very modest concentrations compared to the fission products. Soon there began to be assessments of potential health effects of the actinides through hundreds of human generations, e.g., Barr (1974). The inhalation pathway was still prime for early exposures, but ingestion became of importance as time progressed. This is shown in figure 15.10, taken from Barr.

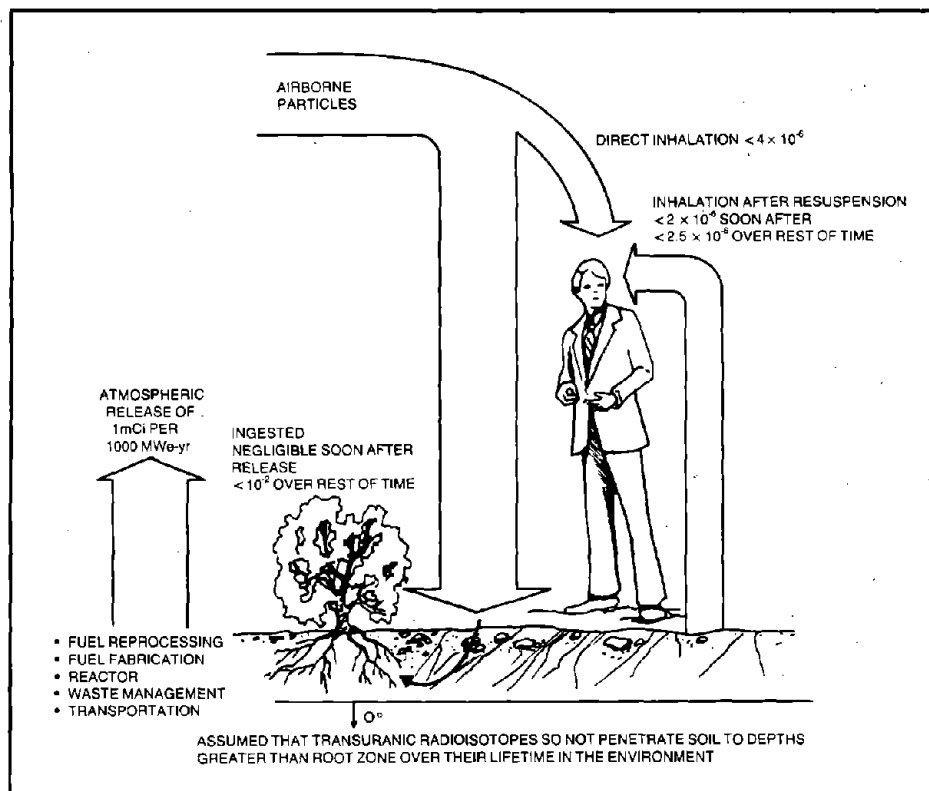


FIGURE 15.10. Summary of major routes to man. The expression "MWe-yr" means megawatts electrical energy each year. (Redrawn from Barr 1974.)

Note that the increased significance of ingestion may require hundreds or even thousands of years to take over from inhalation.^(a) Also, because of greater absorption from the gastrointestinal tract, nuclides other than plutonium (e.g., ^{241}Am , ^{237}Np) may become the largest contributors to dose.

Considerable interest has been attached for many years to areas with high levels of naturally-occurring radionuclides, principally near the surface. Much work has been done to determine, if possible, any ecological or population effects of the high external radiation dose associated with these. Two areas have been studied in most detail, one in India, the other in Brazil. The one in Brazil has contributed information of great interest to the problem of radionuclide transfer in the environment and of radioactive waste disposal.

Eisenbud has worked for many years with Brazilian colleagues to study the translocation of thorium and rare earth elements from a rich deposit in the state of Minas Gerais, Brazil. The results indicate almost total immobility for these isotopes. Let us see by quoting the abstract from a recent paper by Eisenbud and several colleagues (Eisenbud et al. 1984):

A highly weathered deposit of thorium and rare earth elements located near the summit of a hill in the state of Minas Gerais, Brazil, is being studied as an analogue for a radioactive waste repository that sometime in the distant future may be eroded to the surface or intruded by groundwater. Thorium serves as an analogue for Pu^{4+} , La^{3+} as an analogue for Cm^{3+} and Am^{3+} . The mobilization rate constants of the analogue elements by groundwater are so slow (of the order of 10^{-9} per year) as to suggest that essentially complete radioactive decay of the transuranic actinides would occur in place even under the relatively unfavorable conditions that exist at a site such as this.

These conclusions were expanded and strengthened by an erudite and convincing summary given by Eisenbud at a recent annual meeting of the NCRP (Eisenbud, Linsalata, and Franca 1985). If these phenomena can indeed apply to plutonium and related actinides, there should be a significant impact on waste considerations.

Details of radioecology studies on transuranics in the environment can be followed easily in the very useful review chapter by Watters et al. (1980) at the beginning of the book edited by Hanson (1980) and in the Snowbird actinide symposium (Watters 1981); also in the proceedings of the ERDA workshop at Seattle, cited in an earlier connection (ERDA 1976), and in briefer form in the book by Kathren (1984). In the chapter in Hanson (1980) there is a review of solubility and chemistry of plutonium and other actinides using data originating in a variety of laboratories for both aquatic and terrestrial systems, behavior in freshwater and marine environments, including the role of phytoplankton, the transfer in dust and soil, including the phenomena of resuspension, to be reviewed presently, and prediction of long-term behavior. Also, Durbin prepared a chemically oriented review of the transfer of plutonium to plants from soil that brought together data from many sources (Durbin 1974). The sources of data for these works include some old friends, U Pond at Hanford, White Oak Lake at Oak Ridge, several ponds and reservoirs at Rocky Flats. There are also

(a) Let us not neglect inhalation because of the realization that other pathways may play a part someday. One needs only to review the data presented by Bair (1974) at the same symposium as the Barr calculations to be convinced again of the potency of plutonium as a pulmonary carcinogen.

some new sources, e.g., canals, ponds, and the Miami River at Miamisburg, Ohio (Mound Laboratory); the Great Lakes; the Hudson River; the Savannah River; several Canadian lakes; and some ponds and lakes in the southeastern United States, to name a few.

There are complexities of detail. Concentration factors obtained in laboratory studies (chapter 13 and Price 1973) were one to two orders of magnitude lower than those found in field studies, both at Oak Ridge and NTS. A typical example taken from the work at UCLA and at NTS is shown as table 15.7. In each case, an increase in mobility with time appeared in the field work.

TABLE 15.7. Comparison of Plutonium Concentration Ratios for Field and Glasshouse Conditions

Soil Source	Field	Glasshouse
NTS Area 11B	1.3×10^{-2} to 1.6×10^{-1}	1.5×10^{-4}
NTS Area 11C	4.5×10^{-2} to 3.4×10^{-1}	1.8×10^{-4}
NTS Area 13	7.8×10^{-2} to 4.4×10^{-1}	1.1×10^{-4}

NTS (Nevada Test Site).

Source: Modified from Romney and Wallace 1977 by Watters 1981. Reprinted with permission of RD Press, University of Utah, Salt Lake City, Utah, copyright 1981.

Higher concentration ratios for plutonium, e.g., 10^{-3} to 10^{-4} , were found in the arctic tundra system discussed above in connection with cesium (Hanson 1980). Two relatively recent reports show both the present status and the development of information on alpha emitters in the Arctic. One is from Finland (Jaakkola et al. 1981), supported by DOE. The other is from the University of Lund, Sweden (Holm and Persson 1981). However, before we get too excited about plutonium and the actinides in Arctic systems, we should compare them with the naturally occurring activity concentrations of ^{210}Po in the lichens. The data are shown as table 15.8. Obviously, ^{210}Po is the predominant alpha-emitting radionuclide in this system!

Both field and laboratory experiments showed marked differences among the actinides. For uptake by terrestrial plants, the order of uptake was $\text{Np} > \text{Cm} > \text{Am} > \text{Pu}$ (Price 1972; Schreckhise and Cline 1980; Kathren 1984). Neptunium could be from 2,200 to 45,000 times as mobile as plutonium (Kathren 1984).

Because of an increase in the recommended absorption factor (ICRP) for neptunium from the gastrointestinal tract, ^{237}Np became theoretically the controlling nuclide in high-level waste after several thousand years. The validity of this development has been questioned and is being examined in depth, particularly by Maurice Sullivan and Roy Thompson at PNL and the group at ANL through a task group of the NCRP (see review by Thompson 1982a).

Other members of the actinide group, such as uranium and thorium, have been cast in a different light. There is already an ample quantity of these in the earth's crust, and they are uniformly present in natural ecosystems. Because of their long half-lives and low level of radioactivity, they have not been considered as seriously, as environmental contaminants, as the elements mentioned above. Yet, as we will discuss presently, there is now considerable interest in

TABLE 15.8. Alpha-Emitting Nuclides in the Lichen *Cl. Alpestris*. (The values are representative for 1972.)

Nuclide	Activity Concentration	
	(pCi/kg dry weight)	Bq/kg dry weight
²¹⁰ Po	7000 ± 1000	260
²³⁴ U	5.6 ± 1.1	0.2
²³⁵ U	0.2 ± 0.1	0.007
²³⁸ U	5.4 ± 1.0	0.2
²²⁸ Th	3.4 ± 0.6	0.13
²³⁰ Th	1.9 ± 0.4	0.06
²³² Th	1.7 ± 0.3	0.06
²³⁸ Pu	6.3 ± 0.5	0.23
²³⁹⁺²⁴⁰ Pu	140 ± 10	5.2
²⁴¹ Am	30 ± 3	1.1
²³⁷ Np	0.4 ± 0.1	0.01
²⁴² Cm	0.006 ± 0.002	0.0002
²⁴⁴ Cm	0.006 ± 0.002	0.002

Source: Reset from Holm and Persson 1981. Reprinted with permission of RD Press, University of Utah, Salt Lake City, Utah, copyright 1981.

standards for uranium in drinking water (Wrenn 1984; EPA 1981a,b), and its movement in the environment has been taken up in several laboratories in the United States.

In general, uranium is considerably more soluble than plutonium.^(a) A concentration factor of unity is usually assumed for it (Kathren 1984). Thorium compounds tend to be much less soluble than uranium salts.

Finally, it should be mentioned that metabolic modeling for the actinides has begun in earnest. For many years, we had only a model for uranium developed by Struxness et al. (1956) for the first Atoms for Peace Conference and reviewed by Durbin and Wrenn (1975) at the Arlington, Virginia, conference on uranium. There was reluctance to attempt much for the higher actinides. After all, the blue ribbon task group of ICRP that prepared Publication 19 on plutonium (ICRP 1972) could not establish a general metabolic model for the actinides in bone, even though the group working on alkaline earth metabolism could present a detailed model in ICRP Publication 20 (ICRP 1973, the "Marshall model").

In the late 1970s, various groups, particularly the one at the University of Utah, seemed to feel it was time to attempt some general metabolic modeling for the actinides, including models that would tie into environmental transfer. Accordingly, at the Actinide Workshop at Snowbird, Utah (Wrenn 1981a), a full session was devoted to actinide modeling. It contained a comparison of the metabolism of plutonium in dog and rat by Mahaffey and the group at PNL^(b) (Mahaffey et al. 1981); an in-depth discussion of retention factors, with a brief

(a) Remember the problem of leakage of uranium and other radionuclides from uranium mill tailings described in chapter 11?

(b) They also related the differences in metabolism to the incidence of tumors.

discussion of those for the actinides by Skrabble, Chabot, and Johnson (1981) from the University of Lowell; an URN-model^(a) approach to actinide metabolism by Bernard (1981) at Oak Ridge; and a more conventional mathematical model developed by Cuddihy (1981) at Lovelace. Some of the models are so complex that combining them with an environmental transport model seems almost impossible. Yet, although no one felt the ultimate model was yet ready, there was general optimism that progress was being made.

Wrenn and Durbin, at Utah and Berkeley, have been working on a revised metabolic model for uranium that could be appropriate for environmental intakes;^(b) they have published or presented at meetings its general development (Wrenn, Lo Sasso, and Durbin 1977; Wrenn 1981b; Roswell and Wrenn 1980; Wrenn and Roswell 1980; Durbin 1986). The principal change from earlier models such as those promulgated by the ICRP and NCRP resides in the factor for uptake from the gut. As already noted, and to be seen later in this chapter in connection with the setting of standards for surface contamination, a new metabolic model for uranium would be very timely.

Although models for the transfer of transuranics in the environment may have had a slower start than many other environmental contaminants, there is ample information now. Also, it has the honor of projecting further into the future than any other environmental transport system and a certain aura of mystery that accompanies calculations extending for thousands of years into the future.

There is much yet to be done, however. Watters (1981) outlined at the Snowbird meeting four lines of investigation needing attention:

1. more information on neptunium, americium, and curium
2. determination of the chemical species (presumably the predominant one) in the environment and kinetics of their formation
3. more information for the ingestion route and thus more ingestion experiments
4. models for environmental mobilization and transport (Yes, more models!).

There has, of course, been considerable interest in environmental transport of plutonium in laboratories in other parts of the world. We have had to by-pass most of the work since the results are not qualitatively different from those we have been discussing.

G. Miscellany Regarding Food and Water

Before we close out even this all-too-brief description of the genesis of the environmental transport systems, there are dilemmas and contributions that did not fit the categories chosen for use above that should be discussed.

The enormous efforts of federal and other governmental and private agencies in operation of the surveillance networks for measuring fallout in the environment, especially foods and water, were fundamental to all that followed. (See, for example, Federal Radiation Council [FRC] reports in chapter 12.)

(a) Derived from the concept of a container holding different colored balls to represent different atoms in an organ and application of statistical theory to the taking of samples therefrom.

(b) That is, for the absorption factors and other constants that would be consistent with the differences in solubility, etc., sometimes seen after passage through the environment and that could be keyed to the very low concentrations involved.

In many ways, we can be glad that the methodology for measurements of isotopes in animal and plant nutrition had already gotten a good start through tracer chemistry applications before the fallout dimension came on the scene. An example is the summer symposium held at Oak Ridge in 1952, entitled "The Role of Atomic Energy in Agricultural Research" (Comar and Hood 1953). The thrust of this symposium was the uses of isotopes in animal and plant nutrition research and tracer studies of soils and fertilizers. The isotopes were, of course, not those of later interest. They were radioisotopes of normal metabolites like ^{14}C and ^{32}P . Yet, the methodology learned set the stage for the later studies on food and food chains. In it, Comar (1953), just starting his work with the University of Tennessee-AEC Agricultural Research Program in Oak Ridge (see chapter 13), gives basic information on how isotopes can be used for many purposes in agriculture. These included direct movement in environmental media, movement into and within an organism (including incorporation into the organism), measurement of rates of movement, and precautions in the use of isotope methodology.

The first compendia relating directly the transfer of radionuclides to food and water were in the Congressional hearings cited extensively in chapter 12. These were largely in the 1950s and early 1960s.

An important dilemma that coursed through the discussions of environmental transport in these hearings and elsewhere was whether the amount in food, e.g., milk, was related to the rate of fallout or the total cumulative fallout. This was more than an academic question, since predictions had to be based on one or the other, or perhaps both, and predictions were essential. Proportionality to rate of fallout meant that the food pathway was largely dependent on foliar deposition and subsequent processes. Proportionality to total deposition implied the participation of deposition in and transfer from soil as the principal pathway. Remarks on this dilemma appear in the Congressional hearings, but perhaps one of the broadest earlier discussions was in an AEC report prepared by Harold Knapp (see chapter 12) while he was a member of the Fallout Studies Branch of the AEC Division of Biology and Medicine (Knapp 1961). This concerned ^{90}Sr in U.S. milk and food supplies. Knapp used largely the PHS raw milk sampling network and the AEC Health and Safety Laboratory (HASL) results for the analyses of food and milk, and data from the U.S. Department of Agriculture for soil levels. Unfortunately, his conclusions on the dilemma had to be equivocal.

Meanwhile, the British had stated that, at least in 1958, only about 20% of the ^{90}Sr in British milk could have entered the chain by absorption from the soil. *The rest had to be from foliar deposition.* This was discussed early on by Russell (1960) at the Minneapolis symposium and later in the broad-gauge book already discussed on the whole subject of radioactivity and human diet prepared and edited by Russell (1966).^(a) There was a tendency to attribute most of the cesium content of milk to foliar deposition because of its high tendency to complex with and remain in soil. Thus, deposition rate would be the predictive factor for this and many other relatively immobile radionuclides, and the British so stated. However, for strontium under conditions of longer-term deposition, the potential for some contribution from soil could not be gainsaid. As we are already aware, many factors can influence behavior of an element like strontium in soil, and thus make significant differences in its availability to plants.

(a) To indicate the extent of knowledge as of 1966, as perceived in the United Kingdom, the table of contents of this monograph is given as note 3 at the end of this chapter.

The importance of the foliar deposition pathway, recognized by the British in 1958 and emphasized earlier, was put on a more quantitative basis in later studies of Cataldo and Vaughan (1980) working with plutonium aerosols of less than 1 μm . They subsequently showed that the proportion of airborne plutonium isotopes fixed in bone via the ingestion of vegetables is at least one hundred thousandfold larger by the foliar deposition route than it is by the soil uptake route, when dietary and accumulation factors are considered (Vaughan et al. 1981). One may expect foliar deposition to dominate in food chain routes for other radioelements as well.

In 1962, the U.S. National Academy of Sciences (NAS) produced a report published in pamphlet form that concerned fallout radionuclides in food. It was revised and updated in 1972, with less emphasis on fallout and more emphasis on effluents from nuclear reactors and fuel reprocessing (NAS 1973). It provided summaries of natural and manmade radionuclides in food and a discussion of quantitative methods for gamma-emitting radionuclides in food and the characteristics of various sources of contamination. It urged greater consideration of special groups such as fetuses, infants, the infirm,^(a) and the aged. It also urged further investigation of the reasons for variations in movement of radionuclides in the ecosystems and raised questions regarding the validity of basing human tolerance levels on the sensitivity of the measurement systems.

In 1963, the Federation of American Societies for Experimental Biology held a nutrition symposium on the subject, "Fallout, Food and Man" (Federation Proceedings 1963). The Federation includes essentially all of the disciplines characteristic of the basic sciences in medical schools and frequently has attendance figures up to twenty thousand at its meetings. Robert Menzel, from the U.S. Department of Agriculture at Beltsville, Maryland, reviewed the pathways by which plants can become contaminated with fallout nuclides and considered the quantitative effects of various factors. He pointed out that about 1% of the strontium in surface soil may be taken up by a single crop, while the figure for radiocesium and most of the other fallout nuclides being considered then was 0.1% or less (Menzel 1963). Field work showed that corn, soybeans, oats, or wheat took up from one-third to two-thirds as much radiostrontium when it was placed twenty inches below the surface, as from a conventional plowed layer. Work in England also showed significant differences in uptake as a function of the placement in the soil, especially with reference to the root zone.

At the same symposium, Comar (1963) reviewed factors influencing the biological availability of fallout radionuclides to animals and man. Eisenbud (1963) was careful to point out that, despite emphasis in current thinking on the introduction of manmade radionuclides, naturally occurring radioisotopes, such as ^{40}K , ^{226}Ra , etc., contribute by far the largest portion of radioactivity present in our foods. He pointed out that the uranium and thorium chains together include twenty-five isotopes of ten elements, and it was only in the previous few years that their distribution in foods had been subjected to careful investigation on both sides of the Atlantic.^(b) He also presented summary information on the work of HASL on strontium, cesium, and iodine.

(a) It is to be noted that even present-day transfer models do not include any modifications of input parameters for abnormal physiological or metabolic situations, as might occur in the infirm.

(b) These are mostly alpha emitters and not likely to be confused with fallout radionuclides in environmental measurements, but their transfer processes are pertinent to the general picture.

Read (1963), from the National Dairy Council, discussed countermeasures against fallout in foods. This is beyond our scope here but is mentioned because it constitutes a good summary of the many ideas extant.

The fact that these discussions took place well outside what we have referred to as "the internal emitter establishment" is an important indication of the breadth of talent brought to bear on transfer of radionuclides to foods and water in those years when the basic data behind our present systems were being gathered.

As we pointed out in chapter 12, most of these enterprises wound down in the middle and late 1970s because the levels of fallout in food and other samples were below the limits of detection. The exception is, of course, the long-lived actinides and the discernment of radionuclides from sources such as high-level waste storage areas, uranium mill tailings, etc. However, these are local problems that do not have much bearing on generalized food contamination. The emphasis has changed. The federal establishment must review and help prepare current environmental impact statements for planned facilities. It must review the performance of operating facilities. To do this, competence in the field of environmental transfer factors has had to be maintained. Thus, the *dramatis personae* are now largely in the NRC and the EPA.

The EPA is continuing analyses of samples of air, milk, and water at its Eastern Environmental Radiation Facility in Montgomery, Alabama. The results are issued quarterly in an environmental radiation data report. It will be noted, however, that this effort apparently does not include foods other than milk. An important summary of population doses from many categories of ionizing radiation in the United States was issued by the EPA in 1977 (EPA 1977b). It will be described in more detail in the next section.

In 1972, the EPA issued a guide for environmental radioactivity surveillance. At the time, the EPA viewed surveillance of nuclear facilities as part of its responsibilities and aimed the guide primarily at work outside the plant-site boundary of a light-water-cooled reactor.^(a) While intended as an operating guide, the document presents much information on pathway analysis, generation of models, detection capabilities, and related information that is not usually found in a single document (EPA 1972).

Much current energy is now going into the development of prospective standards for environmental contamination, both in general and for specific elements. We will review some of this effort and its background in the next major section of this chapter.

IV. Population and Environmental Dose Assessment, Resuspension, Standards for the Environment

A prime objective of all the work on environmental transfer factors for radionuclides is an ability to assess the radiation dose to humans or occasionally some other critical segment of the environment. Another objective is to set limits and to be able to measure compliance with those limits. Calculation of dose to populations or individuals in populations has been engaged in rather generally, although many uncertainties prevail. The design of a sophisticated system for

(a) The NRC has primary responsibility for surveillance inside the boundary and there was some dissatisfaction with having EPA set out an independent guide, but the problem seems to have been accommodated. More later.

setting standards for population exposure has remained elusive. We are still leaning mostly on the use of a scaling factor from occupational dosage limits, with the exception of some special cases such as effluents from light-water-cooled reactors, the uranium fuel cycle, and water standards in the environment. In this section, we will review some of the work that has been done in this area by adding some generalized concepts developed over the years and some landmark documents. There is considerable extension from environmental transfer factors *per se* to standards derived for environmental exposures derived in part from these factors.

A. Population Dose Assessment

Population dose assessment is a much older activity than population dosage standards. Obviously, the primary thrust of the fallout measurements in the 1950s and 1960s was assessment of the possible dose to humans or to critical components of the environment. Prior discussions in this and previous chapters have supplied ample illustrations. We refer the reader to chapter 12 for details.^(a) It was a universal effort. The same can be said for the evaluation of the possible impacts of the operation of nuclear facilities (chapter 11). In the late 1960s and early 1970s, there was a veritable explosion of population dose assessments and projections. Part of this came about because of the passage in 1969 by the U.S. Congress of the National Environmental Policy Act and the generation, beginning in 1970, of the need for environmental impact statements for everything from a proposed small facility to the operations of a whole industry. It has been a joint effort of industry and government, with government doing the very large studies, but industry required to do quite complicated analyses for any facility they proposed to build (and there were many of them in those days).

A moderately early example of efforts to estimate population doses from the operation of nuclear facilities in the United States was the so-called "Year 2000" study. The AEC sponsored this study through the Hanford Engineering Development Laboratory with the assistance of the Battelle Memorial Institute and the AEC Division of Reactor Development and the Director of Regulation. It was started in the late 1960s, when nuclear power for electricity was considered the wave of the future, and it concentrated on nuclear power facilities. Plans for nuclear power in a specific area—the upper Mississippi and lower Missouri River Basins—were built into computer codes. Like the more general Lawrence Livermore work cited earlier, exceptional care was taken to include all radionuclides and all associated pathways. The study was issued by AEC as a voluminous and very informative in-house report (AEC 1973). An abridged version was presented by Saul Strauch, of the AEC Division of Reactor Development and Technology, at the Third National Symposium on Radioecology held at Oak Ridge in May 1971 (Strauch 1971). The dose calculation model was, as presented, probably one of the most comprehensive to be included in one document up to its time. It is shown as figure 15.11.

(a) Remember that the concept of dose commitment (chapter 16 and later sections of this chapter) was introduced by UNSCEAR in 1962 from ideas generated by Bo Lindell as a means for evaluating the public health significance of the fallout from nuclear weapons testing.

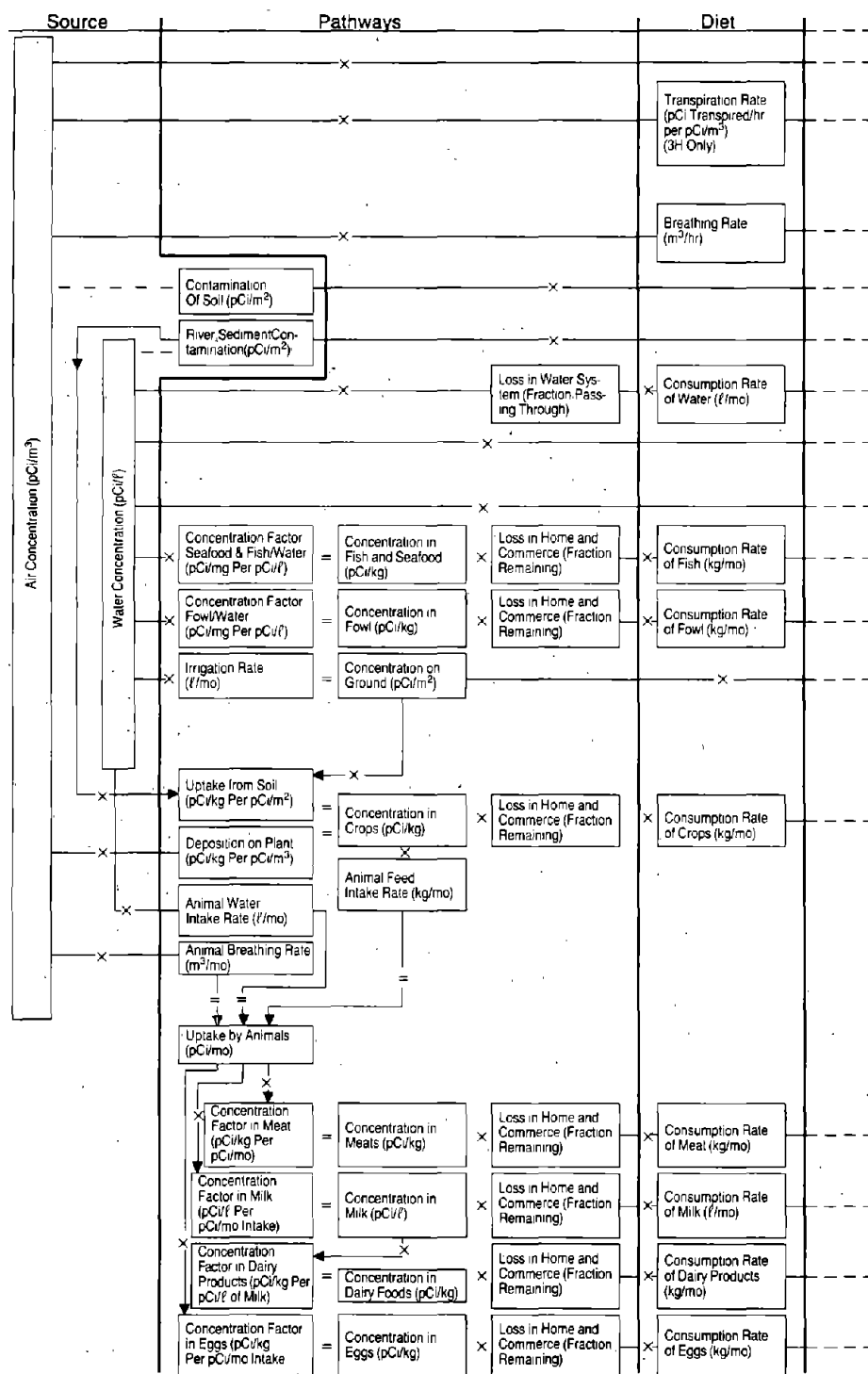


FIGURE 15.11. Dose calculation model. (Redrawn from Strauch 1971.)

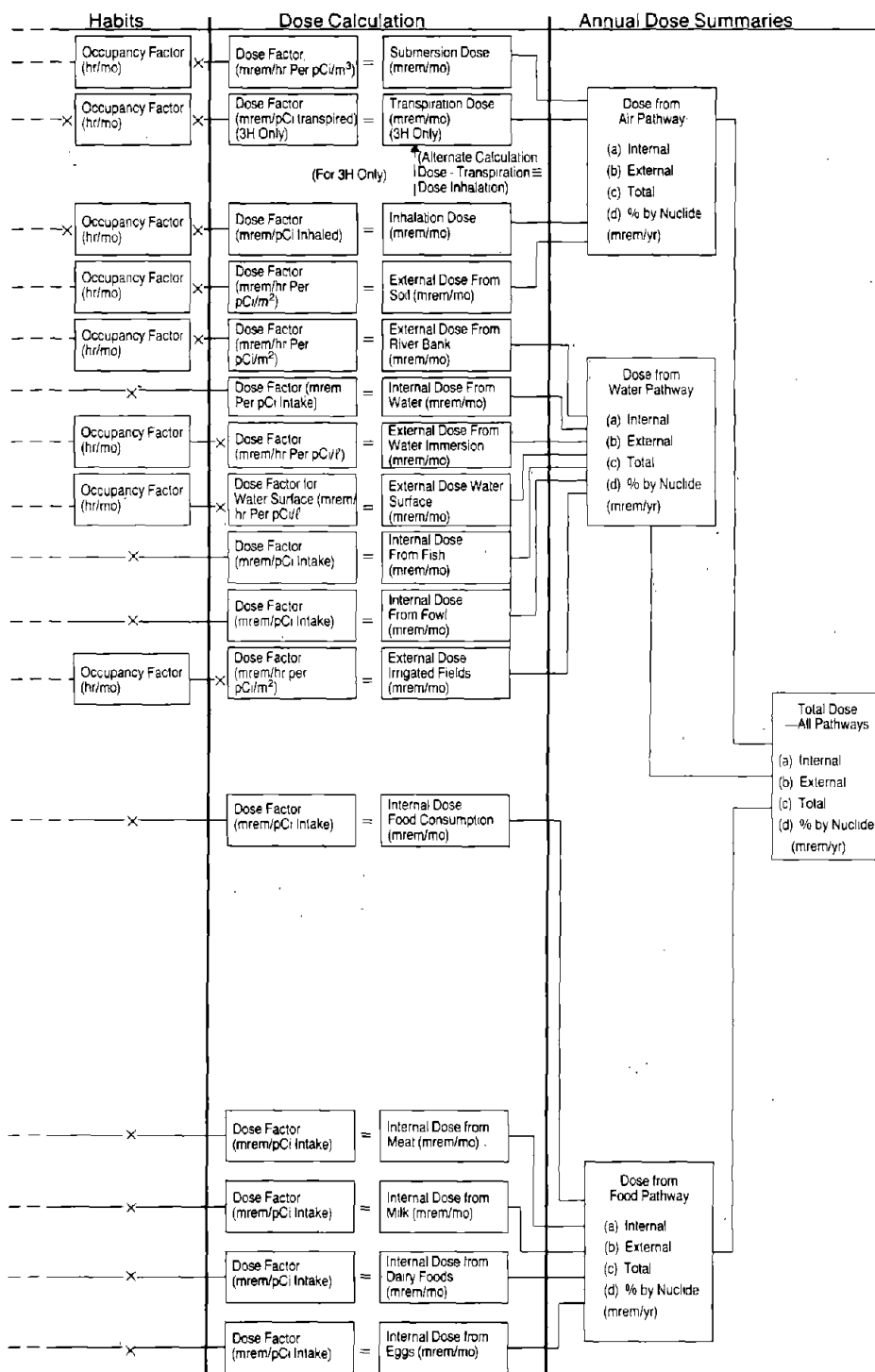


FIGURE 15.11. Continued

In order to get to the source terms, air concentration and water concentration models had to be developed for different reactor types, for processing plants, etc., plus operational factors, a list of food items, a living pattern data flow; in toto, enough to choke the best computers of the day, although no problem for current models. Unfortunately, the quantitative answers from this study are not germane now because the projections for nuclear facilities were far greater than what actually developed. The actual doses will be significantly lower. Nevertheless, the methodology could be applied to revised scenarios, and has been, with modifications, by the currently active agencies. A few of the highlights are presented below:

1. Despite variable contributions to specific organs from specific radionuclides and from more than one pathway, the radiation dose to the population involved was governed to a considerable extent by air transport. Water and food transport played less important roles. The relative contributions of various pathways for total body and six organs are shown as figure 15.12.

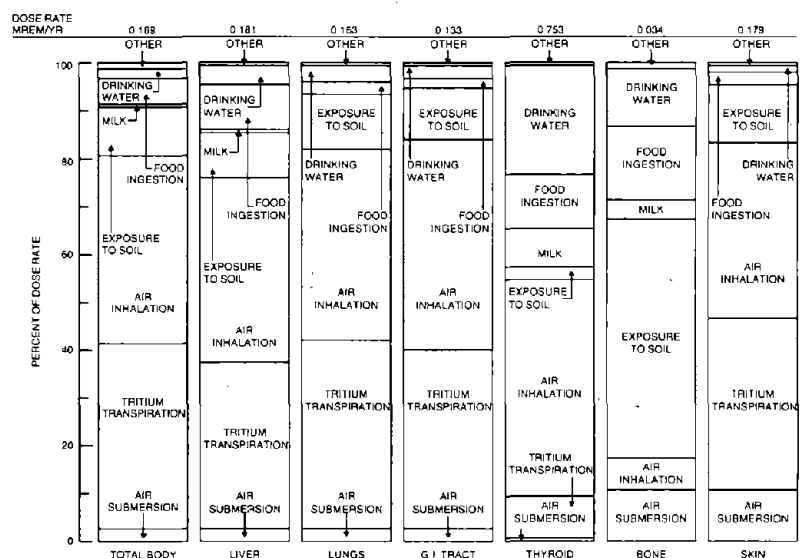


FIGURE 15.12. Contributions by pathways (average individual). (Redrawn from AEC 1973.)

Note that tritium transpiration plays an important role for most pathways and that it is considered an air pathway. The item "exposure to soil" is regarded as external radiation from nuclides deposited in soil.^(a)

2. The contributions from the many nuclides involved are nothing like those seen with fallout or any general exposure to mixed fission products from nuclear facilities. The reason for this is the degree of containment achieved in normal operations. Thus, the noble gases, the iodines, and tritium are the major contributors, except for bone. Indeed, it is only for bone that strontium and ruthenium appear at all. This distribution, by organ system, is shown in figure 15.13.

(a) The apparently large contribution from this source to bone, seen in figure 15.12, is due to the relatively low radiation dose absorbed by bone from the sources dominant in this study and the fact that the values are relative, i.e., percentage of dose rate.

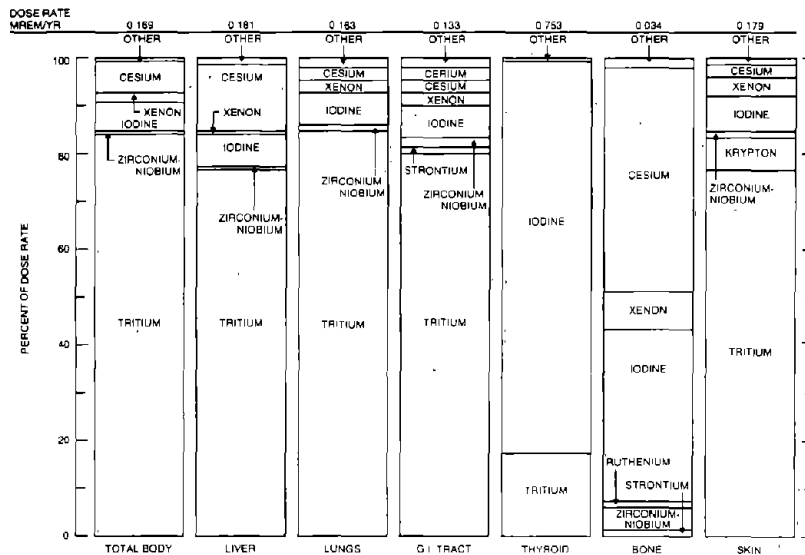


FIGURE 15.13. Contributions by radionuclides (average individual). (Redrawn from AEC 1973.)

It should be understood that this distribution of doses could be entirely different if the study had focused on accidental releases. This was strictly a normal-operation scenario with high factors of containment for most of the "bad actors" seen in fallout or in the release of appreciable fractions of the radionuclides present in a nuclear facility.

3. For bone and thyroid, food and drinking water pathways assumed more importance than for other organs.
4. The generalizations above were for the mix of reactor types projected. To give the reader a base for independent judgment, an elaborate table is included in the report that analyzes the relative contribution of each major radionuclide for different reactor types and for various components of decontamination systems, reprocessing plant operations, etc.

There are a few differences in detail between the full AEC report and the paper by Strauch (1971). They do not modify the principles significantly.

In 1972, the EPA produced a report, *Estimates of Ionizing Radiation Doses in the United States 1960-2000* (Klement et al. 1972). Since this was something of a prologue to a more comprehensive effort published later, we will hold discussion for the present.

The IAEA seminar at Portorož, Yugoslavia, on Population Dose Evaluation and Standards (IAEA 1974) produced a high concentration of workers and papers addressing the general theme of population dose evaluation.^(a)

(a) Because of its applicability to the subject at hand, and to show the extent of the international resources that could be brought to bear, the table of contents of this seminar is shown as note 4 at the end of this chapter.

The dose-commitment approach used for assaying occupational exposure was extended in the early 1970s to population exposure. At the Portorož seminar, Beninson, from Argentina, introduced the term "Collective Dose Equivalent" (Beninson 1974). This was applied to individuals in a group, a subpopulation, or a population. The collective dose was defined as:

$$S = \sum_i D_i N_i$$

where D_i is the dose received by individuals in a group i and N_i is the number of individuals in the group. The answer was in "man-rad" or "man-rem." To get the collective dose *commitment*, an infinite time integral of the average dose rate caused by a given practice or operation multiplied by the size of the population was computed. This was symbolized as:

$$S_C = \overline{\dot{H}(t)} P(t) dt$$

where S_C is the collective dose equivalent, $\overline{\dot{H}(t)}$ is the average dose rate at time t , and $P(t)$ is the size of the population at time t . It was necessary to postulate growth of the population. Beninson postulated exponential growth for the near term at a rate of $2 \times 10^{-2}/\text{yr}$.

Using reasonable assumptions regarding environmental transfer, tissue dosimetry, etc., the collective dose equivalent rates for readily airborne radionuclides were computed. They were relatively large, on a per curie basis, for ^{85}Kr , moderate for tritium, and very low for ^{129}I . The story would have been different if dose commitment rather than dose equivalent rate had been considered, especially over such long integration periods. For example, because of its very long half-life, the dose commitment from ^{129}I would be delivered over many millions of years.^(a) These figures, on a per curie basis, need to be multiplied by source terms such as the release rates per unit of energy generated to give estimates of population dose commitment from the operation of nuclear power facilities, or by measured fallout rates and totals to give estimates of population dose commitment from nuclear testing.

Beninson has been an active member of the ICRP for many years. It is, therefore, not surprising to find that the concept of collective dose equivalent appeared in the revised ICRP recommendations in Publication-26 (ICRP 1977). The quantity was defined, slightly differently than in the Beninson paper at Portorož, as:

$$S = \sum_i H_i P_i$$

where H_i is to *per caput* dose equivalent to the whole body or any specified organ or tissue of P_i members of a subgroup (i) of the exposed population. For a particular practice, with a source (k), the collective dose equivalent was defined as:

$$S_k = \int_0^\infty H P(H) dH$$

where the $P(H) dH$ is the number of individuals receiving a dose equivalent in the range H to $H+dH$.

(a) It will be noted that Beninson chose radionuclides that were easily dispersed in the environment but had from long to very long half-lives. Obviously, an integration to infinity is not very much needed for short-lived radionuclides.

Neither the Beninson paper nor the ICRP definition says much about the environmental dispersion model(s) to put between the source and the final calculation of dose. Apparently, Beninson considered only rapidly dispersing elements and the atmospheric transfer route.

There are few cases where the entire story from release at the source to its final dose commitment is told in equal detail. One moderately complete example can be found in work from Associated Nuclear Sciences in London (Martin and ApSimon 1974). They modeled local doses from a typical U.K. site (probably Windscale) for tritium, ^{14}C , and ^{85}Kr to a standardized critical group, to the U.K. population, and to the global population.

They assumed airborne dispersion and a standard dilution factor of $10^{-7} \text{ sec m}^{-3}$, a 100-m stack, and used Pasquill's methods for calculating dispersion. Of special interest is the twenty-compartment model for ^{14}C they got together for estimating the dose to the global population. This could apply as well to fallout radionuclide dispersion as to a local source and is given as figure 15.14.

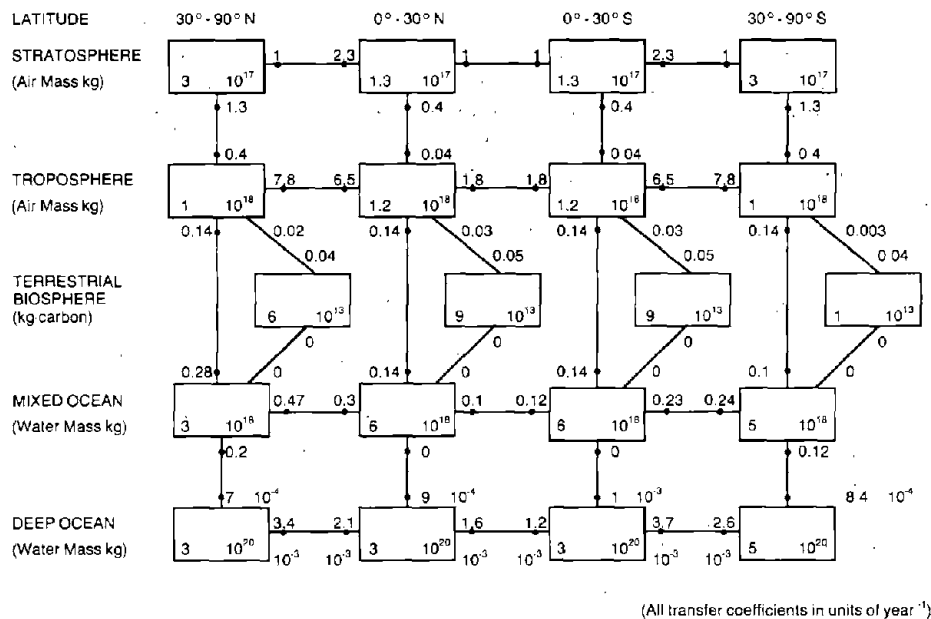


FIGURE 15.14. Global transport model for ^{14}C . (Redrawn from Martin and ApSimon 1974.)

Let us quote the details the authors give about this model.

Four latitude bands are considered, 0° to 30° and 30° to 90°, north and south. Each latitude band is divided into five compartments, namely, stratosphere, troposphere, mixed ocean, deep ocean and a fifth compartment which may represent either the biosphere or surface water. The rates of exchange between atmosphere and ocean or atmosphere and biosphere depend on the physical and chemical form of the contaminant. Within the atmosphere or the ocean, the dispersion of radioactivity depends largely on the natural circulation cycles. The transfer coefficients between the various compartments in the model have been estimated from a review of a number of authors.

In the atmosphere, mixing within each latitude band is quite rapid with time scales of weeks to months. The troposphere is rather shallower at the higher

latitudes than in equatorial regions and mixes more rapidly with the stratosphere. Mixing between the latitudes depends on prevailing wind systems and on Hadley cell circulation. Transfer between the hemispheres takes place both by the mean Hadley cell circulation and by eddies in the upper troposphere.

In the oceanic circulation system, the surface layers down to a depth of 50 to 100 m are well mixed by the influence of winds and surface currents. Residence times in these surface layers are estimated to be a few years. Transfer rates within and from the deep ocean are much slower. During winter in the arctic and antarctic, cold water sinks and a deep water current is induced. The deep water from the arctic flows south at rates as low as one mile per day and resurfaces in the antarctic region. Cold water sinking in the antarctic is even denser and flows underneath the arctic current. Radioactivity penetrating to these deeper layers is likely to remain there for hundreds of years.

(Modified from Martin and ApSimon 1974)

For tritium, they assumed that both ingestion in water and exposure to atmospheric tritium contributed to the dose commitment. They had to modify the atmospheric dispersion model for tritium from that for ^{14}C , not only for the different transfer constants, but because the relative proportion of water vapor in the atmosphere decreases quite rapidly with altitude. Also, tritium is lost from the atmosphere to the land and sea by both rain and dry deposition.

For krypton, the authors could assume simple mixing and circulation in the atmosphere^(a) because of its great insolubility.

The dose commitments from these three radionuclides, using the postulates described in part above, are shown, as calculated, in table 15.9. Note that these figures are per curie of radionuclide released.

TABLE 15.9. Dose Commitments from Unit Releases of H-3, C-14, and Kr-85

Nuclide	Mode of Exposure	Dose Commitment per Ci Released		
		Standardised Critical Group ^(a) (rem)	UK Population ^(b) (man-rem)	Rest of World Population (man-rem)
H-3 Release to Atmosphere	Whole Body	8×10^{-9}	1.1×10^{-2}	3×10^{-3}
	Sea	—	—	2×10^{-4}
C-14 ^(c)	Whole Body	5×10^{-7}	1 (i)	14 (i)
		—	2 (ii)	300 (ii)
Kr-85	Whole Body	1.8×10^{-11}	7×10^{-6}	8×10^{-5}
	Skin	3×10^{-9}	1.3×10^{-3}	1.5×10^{-2}

Notes a. Based on dilution factor of $10^{-7} \text{ sec m}^{-3}$

b. Including first pass and subsequent exposure.

c. Dose commitment to i) 30y, ii) infinity.

Source: Modified slightly and reset from Martin and ApSimon 1974.

In these calculations, the build-up of dose (whole-body average) for ^{14}C from world nuclear power programs goes from 10^{-6} rem/yr in 1970 to about

(a) That is with the air masses in the normal atmospheric circulation system.

8×10^{-4} rem/yr by the year 2020. Then assuming no further release after 2020, there is a gradual decay (in two steps) back to about 8×10^{-6} in 10^4 yr.

Also, in 1974, the EPA produced an approach that they called "Environmental Radiation Dose Commitment." They applied it to the nuclear power industry (EPA 1974). This went beyond radiation dose to include potential adverse health effects. In a sense, the concept can be said to represent irreversible public health commitments. They chose four long-lived radionuclide groups: tritium, ^{85}Kr , ^{129}I , and the actinides (^{238}Pu , ^{239}Pu , ^{240}Pu , and ^{241}Pu ; ^{241}Am , and ^{242}Cm and ^{244}Cm). Theoretically, the total population dose was calculated as the sum of all doses to individuals over the entire time period the material remains in the environment in a state available for interaction with humans. However, they eschewed integration to infinity. Even though some of the radionuclides chosen might persist for up to millions of years and might migrate over quite large areas, the EPA investigators felt they could not meaningfully project their persistence in the biosphere for periods longer than a number of decades. They chose one hundred years. This may well be because they were in a good position to appreciate the problems of long-term extrapolation from our current environmental models. They also chose to consider potential consequences of only the next fifty years of nuclear operations of the U.S. nuclear power industry.

The mathematical expression for the cumulative population dose was not dissimilar from those quoted earlier, except that it had overt terms for a pathway model conversion factor and a dosimetry conversion factor. It is as follows:

$$D_i(t) = \sum_{n=0}^{\infty} Q_i(t) e^{-\lambda_i n} T_i(n) F_i P(t+n)$$

where $D_i(t)$ = cumulative population dose resulting from the release of radionuclide i in calendar year t

$Q_i(t)$ = quantity of radionuclide i released in the year t

λ_i = radioactive decay factor for radionuclide i

$T_i(n)$ = pathway model conversion factor relating quantity of radionuclide i released to its concentration in the medium at the location of interest n years following release

F_i = dosimetry conversion factor relating concentration of radionuclide in the medium to resultant dose to individuals exposed

$P(t+n)$ = number of persons exposed in calendar year $(t+n)$

t = calendar year of release

n = number of years from year t

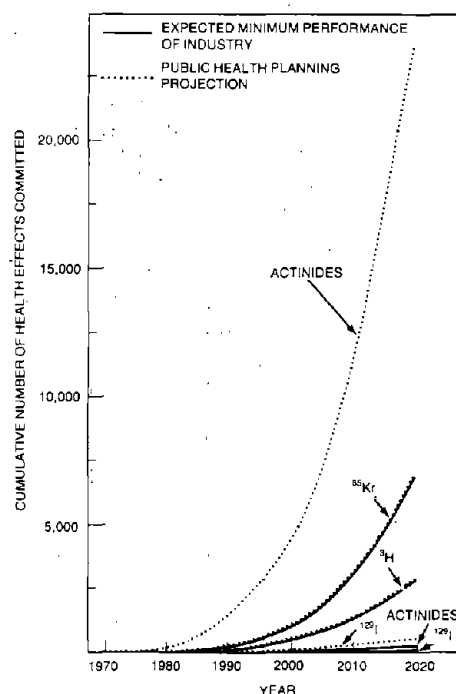
This illustrative expression is necessarily simplified. In real applications, the complications introduced by the multiplicity of environmental pathways, differences in doses to various organs, and the spatial dependence of both the pathway model and population must be considered explicitly. This expression applies specifically to the situation in which exposure of all individuals is uniform and the dose of interest is to the whole body, or to one organ, and from one medium only. Appendix A contains more detailed general equations, which consider the complications introduced by the above and other factors. (EPA 1974)

For the health effects, they limited themselves to estimates of cancer and serious genetic effects and used risk coefficients from the 1972 NAS BEIR report. As a further exercise, the EPA analysis chose to try two release fractions for the four radionuclides: (1) those associated with what they termed "expected minimum performance," a somewhat confusing term that meant expected normal minimum releases; and (2) a "public health planning" value that ranged from no change to a factor of one hundred higher in the release fractions (see below).

The report is very useful in giving numerical values for all of the key parameters and, in Appendices, the derivations of the conversion factors for pathways and for dosimetry. Again, the results are not quantitatively useful now because the projections were for a much larger U.S. nuclear power industry than we have. Yet, they are informative in principle and for the methodology. Obviously, any recalculations would probably produce lower values because of the lower source-term figures.

Upper estimates for fifty years of operation showed as many as five thousand to twenty-five thousand committed potential health effects over the succeeding one hundred years. Tritium and krypton produced about the same number of projected effects when normal operations and containment were assumed, and were higher than the actinides. However, the actinides overwhelmed the system for future effects when the "public health" set of criteria was applied.^(a) This somewhat startling difference is shown in figure 15.15

FIGURE 15.15. Estimated cumulative potential health effects committed by projected releases from the U.S. nuclear power industry. (Redrawn from EPA 1974.)



The primary reason that tritium and krypton release fractions do not change in the above calculations is that they are not trapped in present nuclear fuel cycle operations, while iodine and the actinides are normally contained to a very considerable extent.^(b) Nevertheless, the EPA workers take the view that

- (a) It is not clear whether or not the public health criteria were a "worst case" situation. The release fraction for tritium and krypton was taken as 1 for both sets of conditions, while those for ^{129}I were 10^{-3} and 10^{-1} , respectively, and for the actinides 10^{-7} and 10^{-5} for release fraction and 10^{-8} and 10^{-6} , respectively for resuspension (per meter). We will discuss resuspension presently.
- (b) Brodsky (1980) has examined the probabilities of intake by humans of materials potentially available from a number of operations and has found a strong tendency for the fractions to be in the neighborhood of 10^{-6} . While this cannot be a universal number (accidents do happen), Brodsky raised the question as to whether or not it was a "magic number" that could be applied fairly generally for release fractions of all but nuclides like krypton, tritium, etc.

the number of potential health effects for ^{85}Kr (figure 15.15) indicate that means should be introduced to trap it, even though they might be very expensive.

Also, in 1974, the East Tennessee Chapter of the Health Physics Society sponsored a midyear topical symposium on population exposures (Hart, Ritchie, and Varnadore 1974). The participants were a representative cross section of individuals and laboratories active in the field. There were sessions devoted to historical development, the contribution of background radiation exposures, medical radiation exposures, nuclear power exposures, exposures from fossil fuels, consumer products, nonionizing radiation, dosimetry, and a public forum on population exposures from nuclear and nonnuclear electric power generation. Among the papers pertinent to our present discussion is a critical appraisal of population health risks from power plant effluents by Andrew Hull from Brookhaven (Hull 1974). It takes the view that the Appendix I reductions of population exposure guidelines are unnecessarily low (see section III E 3 and IV D). There is also a review by Golden and Pavlich from Commonwealth Edison in Chicago of population doses from the operation of the Dresden and other power reactors in their network (Golden and Pavlich 1974); estimates of population doses from LWR fuel cycle facilities in operation, and calculated long-term population dose following cessation of plant operations done by the group at Oak Ridge (Witherspoon 1974 and Witherspoon and Parzyck 1974); and several others.

Toward the end of its existence as a federal agency, i.e., just before it was split into ERDA and NRC, the AEC launched an environmental survey of the uranium fuel cycle. The final report^(a) was issued by the Directorate of Licensing (AEC 1974b). (Yes, it was in 1974!) It added consideration of the environmental aspects of the entire uranium fuel cycle to reviews of applications to build and operate light-water-cooled nuclear power plants. It included the "environmental costs" of mining and milling, production of uranium hexafluoride, enrichment, fuel fabrication, reprocessing of used fuel, management of both high and low-level radioactive wastes, etc. These went into the cost-benefit analysis required for the environmental reports and statements, yet it stuck primarily to dose, not to risk or health effects criteria.

Obviously, these broad views of what was needed for planning, if applied literally and conscientiously, could add immeasurably to the cost and complexity of planning and building a nuclear power plant. They did. The counterpart in other areas would be as if all of the problems of mining of coal or production of oil, their transportation and storage, disposal of ash and flue gases, were folded into the plans for building a fossil fuel power plant. It was an important gesture to the total impact of an industry on the environment and was very complete. (Table S-3 of the report requires several pages simply to summarize the considerations.) However, it cannot help but be viewed as the beginning of a much more complex era for not only the nuclear power industry, but, if fairly applied, to all of industry. The recommendations became a part of the code of Federal Regulations (Part 50) in June of 1974. The EPA picked up the thread and produced a set of standards for the uranium fuel cycle that we will consider in section C of this part.

(a) There was a preliminary report in 1972.

This one step could, if properly implemented, absorb all of the fully trained environmental scientists extant with any knowledge or interest in radioactivity or nuclear energy matters. There were a lot of instant environmentalists generated in those days!

Clearly, 1974 was a banner year for estimates of population dose!

Three years later, probably one of the most complete assessments of population doses from a broad spectrum of sources appeared in an EPA document on the radiological quality of the environment in the United States (EPA 1977b). It was edited by K. L. Feldman, required a dozen in-house individuals to comb the literature, and covered both external and internal radiation sources. It is divided into the following categories:

1. Ambient Ionizing Radiation
2. Technologically Enhanced Natural Radiation (i.e., radiation from naturally occurring radionuclides released or at least disturbed and redistributed from their natural repositories by the work of humans)
3. Fallout
4. Uranium Fuel Cycle
5. Many sources such as other federal facilities, radiopharmaceuticals, medical radiation, occupational and industrial radiation, consumer products, and nonionizing electromagnetic radiation.

In a single summary table, both the individual and population dose from each source is given, broken down into external and internal radiation sources. It is of interest that cosmic radiation and medical radiation turn out to supply the principal external dose to the population, while technologically enhanced natural radiation, especially radon and its decay products, supplies the largest population dose from internal sources. The table is reproduced here as table 15.10.

TABLE 15.10. Summary of Dose Data from all Sources, United States

Source	External		Internal	
	Individual Dose (mrem/y)	Population Dose (person-rem/y)	Individual Dose (mrem/y)	Population Dose (person-rem/y)
Ambient ionizing radiation	—	—	—	—
Cosmic radiation	41-45	9.7×10^6	—	—
Ionizing component	28-35	9.2×10^6	—	—
Neutron component	0.33-6.8	4.9×10^5	—	—
Worldwide radioactivity				
Tritium	—	—	0.04	9.2×10^3
Carbon-14	—	—	1	—
Krypton-85	0.035*	—	—	—
Terrestrial radiation	30-95	—	18-25	—
Potassium-40	17	—	16	—
Tritium	—	—	4×10^{-3}	—
Carbon-14	—	—	1	—
Rubidium-87	—	—	0.6	—
Uranium-238 series	13	—	2-6*	—
Thorium-232 series	25	—	7*	—

TABLE 15.10. Continued

Source	External		Internal	
	Individual Dose (mrem/y)	Population Dose (person-rem/y)	Individual Dose (mrem/y)	Population Dose (person-rem/y)
Technologically enhanced natural radiation	—	—	—	2.73 x 10 ⁶
Ore mining and milling	—	—	100,000*	—
Inactive uranium mill tailings piles	—	—	b140-14000	c2.5-70000
Phosphate mining & processing (occupational)	10-300*	—	b6,000*	—
Fertilizer	1.7*	—	—	—
Thorium mining and milling	—	—	—	—
Radon in potable water supplies	—	—	b4,000 d(1,250)*	—
Radon in natural gas	—	—	b15-54	2.73 x 10 ⁶
Radon in liquefied petroleum gas	—	—	1-4	30000
Radon in "health" mines	—	—	—	—
Radon daughter exposure in natural caves	—	—	—	—
Radon and geothermal energy production	—	—	—	—
Radioactivity in construction material	—	—	—	—
Airplane travel	—	—	—	—
Jet (cosmic), per trip over Atlantic	2.6 (500-crew)*	—	—	—
SST (cosmic), per trip over Atlantic	2.0 (1,000-crew)*	—	—	—
Coal-fired electric generating station	—	—	5-70*	0.12-2 x 10 ⁶ *
Oil-fired electric generating station	—	—	0.04*	15*
Fallout	e~2	—	—	—
Uranium fuel cycle	—	2014	—	—
Mining and milling	—	—	f4.5 x 10 ⁻²	2.5
Fuel enrichment	g<0.1	<0.1	h0.3	i0.64
Fuel fabrication	—	—	j2 x 10 ⁻⁴	j0.66
Power reactors	—	—	—	—
BWR	k76 max	m1564	—	—
PWR	k4 max	m21	—	—
Research reactors	—	—	—	—
Transportation	—	—	—	—
Nuclear power industry	—	n100-9600	—	—
Radioisotopes	—	n<170	—	—
Reprocessing and spent fuel storage	p6	p23	p14-257	—
Radioactive waste disposal	—	—	—	—
Federal facilities	—	q480	—	—
ERDA	k<0.1-258	<1-180	—	—
Department of Defense	<0.01	—	—	—

TABLE 15.10. Continued

Source	External		Internal	
	Individual Dose (mrem/y)	Population Dose (person-rem/y)	Individual Dose (mrem/y)	Population Dose (person-rem/y)
Accelerators	^k 0.04-4	0.4-65	—	—
Radiopharmaceuticals	—	^r <0.1	—	^s 3.3 x 10 ⁶
Medical radiation				
X radiation	^t 103	14.8 x 10 ⁶	—	—
Cardiac pacemakers	—	—	<5000	—
Occupational and industrial radiation				
BWR	^u 1230	—	—	—
PWR	^u 1080	—	—	—
All occupations	^v 0.80	28,400	—	—
Consumer products	—	—	—	—
Timepieces	^x <0.5*	^y ~6100	—	—
Smoke detectors	^z 0.007*	0.001*	—	—
Artificial teeth	—	—	^{aa} 140-1390*	—
TV	^{bb} 0.025-0.043	—	—	—
Individual exposure (μW/cm ²)				
Nonionizing electromagnetic radiation				
Broadcast towers and airport radars		10		
All sources		0.1-1		

^aMaximum individual dose to skin surface
^bTrachea-bronchial dose
^cLung-rem/y
^dStomach dose
^e50-year dose commitment divided by 50
^fAverage individual lung dose within 30 km
^gMaximum potential exposure per facility
^hMaximum potential exposure
ⁱCumulative exposure per facility within 80 km radius
^jEstimated bone dose within 80 km
^kFence line boundary dose
^mWithin a radius of 80 km
ⁿEstimated for the year 1973
^pFor NFS Reprocessing Plant, West Valley, NY
^q1965 data

^rBased upon data from 5 institutions
^sEstimated 1980 dose
^tEstimated mean active bone marrow dose to adults—mrad/y
^uAverage occupational exposure/y
^vAverage exposure for all occupations & 3.7 • radiation workers/1000 persons in United States
^xFrom digital watches
^yFrom timepieces containing tritium or radium-activated dials.
^zEstimated.
^{aa}Dose to the superficial layer of tissue.
^{bb}5 cm from TV set; units of mR/h.
—No dose data available.
*Indicates new or revised information.

Source: Reset from EPA 1977b.

Please note that the individual doses are in *millirem per year*, while the population dose is in *person-rem per year*, not an integrated dose as seen in examples quoted earlier. They did not use the environmental dose commitment concept since it could apply to only a portion of the data.

This summary has not been updated. The fact that such a review was done by EPA is salutary, but it is hoped that the effort will be continued with periodic updates, especially to add the contributions from radon in homes (discussed elsewhere).

We have already mentioned that the periodic UNSCEAR reports gave population dose estimates for each radionuclide they considered. The most complete reviews were in the 1972 and 1977 reports. They are divided between doses from fallout and those from other sources, and they include comments on the pathways used in the calculations. The doses are given as *individual* doses, i.e., *per caput* doses to members of the population in northern or southern temperate zones or the world population. We have shown illustrations of the results in an earlier chapter.

As we approach the end of the very active decade of the seventies and move into the 1980s, we find the scene shifting back to fallout and away from nuclear power. This is largely because of the retrospective evaluations generated by the litigations described in chapter 12.

The work of the NAEG (chapter 14) and the enormous compilation of information at the Las Vegas information center concerning fallout from NTS (chapter 12) are, of course, primarily aimed at dose assessment; this time retrospective rather than prospective. There was (and is) a formal "Dose Assessment Advisory Committee," whose work was reviewed in chapter 12.

A recent NCRP annual meeting (1983) included updates of some of these evaluations, e.g., Anspaugh and Church (1983) on NTS; Robison (1983) on the Marshall Islands; also discussions of radon in homes (Rundo and Toohey (1983); various manmade sources released into the environment (Jacobs 1983); and general environmental radioactivity (Harley 1983). There was also a review of the assessment work done and projected for Three Mile Island (Daniels 1983); a general update on doses for the nuclear fuel cycle (Kahn 1983); and a review of the uncertainties of the environmental radiological assessment models (Hoffman and Miller 1983). There was, finally, a masterful review by Dunster reassessing the radiological impact of the Windscale Reactor accident (Dunster 1983). All of these depend, to a greater or lesser degree, on the models and transfer function structure we have described in this chapter. The most extensive overt use of environmental modeling and transfer factors occurs in the paper by Robison on the radiological dose assessments of the northern Marshall Islands. The time periods he took for dose integration were thirty years and fifty years. In other words, the focus was on the generation now inhabiting the atolls rather than on all of humanity over all of time. The thirty-year whole-body dose equivalents varied greatly with the atolls and islands.^(a) The maximum occurred on the northern islands of Rongelap (2.1 to 11 rem from all exposure pathways). The minimum was 0.072 to 0.13 rem on the islands of Likiep. The Lawrence Livermore people also produced figures for the maximum annual whole-body dose equivalent rates for uninhabited islands.

The doses and dose-rates were, in general, from 1% to 5% of the federal guideline of 500 mrem/yr above background. The highest estimated dose equivalent for an inhabited atoll was 10% to 50% of the guideline.

(a) The Brookhaven diet gave, in general, higher dose-equivalent rates than the diet developed by the Micronesian Legal Services Corporation, which Lawrence Livermore used.

Many more examples could be cited, but we have seen enough to discern the trend and the mechanisms.^(a) Population dose assessment has been couched officially by ICRP in terms of integration to infinity. Most current assessments seem content to use thirty to fifty years, sometimes one hundred years, or even annual dose rates. There are many problems with the extremely long extrapolations. Mathematically they are easy, but practically, doubts arise about the validity of input figures for the environmental pathways. A lot of geological changes can occur, watersheds disappear and appear, oceans change levels, climates change, etc., over a few million years. For many ordinary problems, there seems to be a tendency to stay with a scenario that can be visualized with a modicum of assurance. Thus, for the present we may be, consciously or unconsciously, enfolded the philosopher's statement: "The study of infinity will require eternity."

B. Resuspension

1. The Problem

We have reserved discussion of this special aspect of atmospheric transfer to put it in juxtaposition to consideration of surface and soil contamination standards. It is an area where the biomedical establishment and physical scientists have worked together, but it is more aerosol physics than biology.

The basic phenomena of resuspension concern the pick-up by wind of particles that have been deposited on the earth's surface. They are a part of the general phenomena of wind erosion that have been broadly investigated since the 1930s. However, special attention was drawn to the possibilities for and significance of resuspension by the deposition of fallout in arid environments, and in recent years the redistribution of long-lived insoluble radionuclides, such as plutonium and the actinides, at weapons testing sites and around high-level radioactive waste disposal areas. We saw some of the practical problems of health implications in connection with the special safety shots described in chapter 14.

Resuspension is not a single process. At small particle sizes ($<50 \mu\text{m}$) it is largely airborne transport; between 50 and $1,000 \mu\text{m}$, it is largely saltation—a leaping or hopping of one particle over another; above $1,000 \mu\text{m}$, it is largely surface creep of the particles.^(b) Obviously, particles larger than about $10 \mu\text{m}$ are of little biomedical concern as inhalation hazards, but they may deposit on vegetation and thus enter a food pathway. The latter is of more importance with the soluble fission products than with the insoluble actinides. Let it be clear that

(a) *Note added in proof:* In 1984, the EPA provided an update of the data shown in table 15.10 and an expansion to individual facilities (EPA 520/1-84-022-1, vols. 1 and 2). The agency also prepared a comprehensive review of occupational exposures in the United States in the year 1980 with a summary of trends for 1960–1985 (EPA 520/1-84-005). These provide new information for dose assessment, particularly in the environs of nuclear facilities, but no disconcerting surprises.

(b) Intuitively, it might be expected that the smaller particle sizes would contribute the most. Field tests indicate a surprisingly large contribution of particle sizes in the range of the saltation mechanism. Evidently, the "hops" can go fairly high, and the particles can be carried off by wind. Also, the larger particles can contribute by dislodging others. The literature on wind erosion shows many instances where saltation predominates quantitatively (Chepil 1945).

resuspended particles can travel long distances from their point of origin, and inhalation of the transported dust has been considered a significant potential hazard.

Interest in doing research on resuspension phenomena with radionuclides seems to have begun at Hanford, but it spread rather quickly to the laboratories involved with the NTS activities. This was in the early 1950s. John W. Healy, a biophysicist at Hanford, can be considered along with some Hanford colleagues (James Fuquay, G. R. Hilst) as having started the ball rolling. A good place to begin is with the review paper by Healy and Fuquay (1958) given at the second Atoms for Peace Conference in Geneva. Here the relationships of wind transport to the general problems of soil erosion are depicted, and the problems of mathematical treatment of the phenomena are made evident. An entity is introduced that relates to the deposition velocity conventions already discussed in connection with the Idaho Falls field work on iodine (CERT tests). It considered the rate of fallout and was termed the "coefficient of deposition." It was defined as:

$$\Lambda = \frac{\text{rate of deposition per unit area of ground per second}}{\text{volumetric concentration per unit volume of air}}$$

Healy and Fuquay also defined a surface pick-up coefficient, K , that was not too different from the resuspension factor we will define presently. It could be evaluated by measurements downwind from sources of particles. They describe two experiments carried out at Hanford in 1954–1955 (Hilst 1955) done to enable order-of-magnitude estimates of this coefficient, using a fluorescent powder with a mass-median diameter of about $7 \mu\text{m}$. The first experiment was designed to measure changes in airborne concentrations over several days. The second experiment studied differences in pick-up rates among different surfaces. In both experiments, the values of K fell between 1×10^{-7} and 9×10^{-8} , the lower figure appearing, as might be expected, from a wet surface.^(a) The Hanford group then used these data and assumptions regarding particle diameter and wind speed to calculate particle concentration and, when combined with information on the biological effects of radioactive particles, an estimate of potential hazard.^(b)

Healy has kept a lively interest in the phenomena of resuspension ever since (e.g., Healy 1976a,b; 1980) and has been a consistent and impressive contributor to the field. This persisted long after his move from Hanford to Los Alamos. (Many of Healy's later contributions were tied to standards for soil, which we will review in the next section.) The Los Alamos group soon joined in (e.g., Langham 1969), and, at Hanford, Kathren (1968) presented a model that we will consider in a later connection.

Those concerned with NTS were aboard also, and the Lawrence Livermore Laboratory, particularly Lynn Anspaugh, began regular contributions, many of which tied in to the work of the NAEC. Practical aspects became part of the work around the Rocky Flats plant (chapter 11), and there were comparisons

(a) These values were at 50 cm above the ground.

(b) This was for an undisturbed area contaminated by radioactive materials. As we saw in chapter 14, much interest was attached also to the effects of human activities, such as vehicular traffic, on resuspension factors.

between the arid environments of the west and the humid environments of the east and southeast.

2. The Resuspension Factor

In the late 1950s and through the 1960s, a strong urge was felt to devise some simple expression for resuspension and, it was hoped, develop a preferred value or a narrow range of values for such an expression that could be used for hazard estimation. Many practical operations depended on such estimates. As a result, a factor somewhat like that described by Healy, but omitting the parameter of time, came into frequent use. It was termed "The Resuspension Factor," R , and was defined as:

$$R = \frac{\text{air concentration in activity or mass units per m}^3}{\text{surface concentration in activity or mass units per m}^2}$$

The units were, of course, m^{-1} .^(a)

The resuspension factor was applied to industrial and commercial environments, e.g., particles resuspended from floors or benches by indoor air agitation or human activities, as well as to the outdoor environment. As might be expected in a situation where the pickup could be markedly influenced by changes in wind speed, the nature of the surface of deposition, and many other factors in the ambient environment,^(b) the range for this factor was found to be enormous, especially in desert environments. Mishima (1964), at Hanford, could find values all the way from 10^{-13} to 10^{-3} m^{-1} . These are obviously extremes.^(c)

As Healy pointed out in a relatively recent review (Healy 1980), the most frequent values for mechanical disturbance were in the range of 2×10^{-6} to $7 \times 10^{-5} \text{ m}^{-1}$ and from 10^{-8} to $2 \times 10^{-6} \text{ m}^{-1}$ for freshly deposited material left undisturbed.

K. Stewart (1964) did some experimental work that led him to conclude that an appropriate average value of the resuspension factor for use in hazard evaluation for both field and laboratory was 10^{-6} (10^{-5} under conditions of moderate activity). This factor was used for developing general guidelines (Brodsky 1980 and work cited therein), although about all that can be said for it is that few figures in normal operations will be much higher, and it is, therefore, conservative. Many, many measurements were made in the environment, particularly at NTS, to evaluate "the" resuspension factor. They sometimes measured factors higher than $10^{-6}/\text{m}$, and Kathren suggested a very conservative value of $10^{-4}/\text{m}$.

If one contemplates what we discussed earlier concerning changes in the availability of surface-deposited radionuclides with time, it should be apparent

(a) Sometimes the original units were cm^3 and cm^2 and the final answer was cm^{-1} . If readers find puzzling inconsistencies in their reading of the literature, they should check the units used by the authors.

(b) As discussed in volume 2 of the Whicker and Schultz book (1982), these include velocity; turbulence; density, which, is in turn a function of temperature, pressure, and humidity; and viscosity among the atmospheric variables; and texture, particle size distribution; cohesiveness, moisture content, topography, surface roughness, and plant cover among the surface variables.

(c) The range for indoor environments was usually much less, and the values tended to be 10^{-6} m^{-1} or lower.

that any given resuspension factor is most unlikely to be constant for any length of time under field conditions. It will be remembered from chapter 14, for example, that Wilson, Thomas, and Stannard (1960) reported an apparent half-life of thirty-five days for the air concentrations of plutonium after the Test Group 57 safety shot at NTS. Langham (1969) used this value in assessing future hazards for plutonium contamination. Kathren (1968) used forty-five days. Any such figures are undoubtedly of only temporary validity. Indeed, like the resuspension factor itself, there is little reason to expect a constant value for the half-life. If values on the order of thirty-five to forty-five days actually persisted, the projected resuspension factors after ten years would be very much lower than are actually found, e.g., 10^{-29} and 10^{-36} m^{-1} for forty-five and thirty-five days half-life, respectively. The lowest value found in practice was developed in work at the GMX site at NTS, where over twenty plutonium safety shots had taken place. The Lawrence Livermore people used Anderson high-volume cascade impactors to resurvey the area in the summer of 1972, about seventeen years after deposition. They found a mean value for the resuspension factor of $3 \times 10^{-10}/\text{m}$. Additional measurements made by Reynolds Electric and Engineering Company gave $2 \times 10^{-9}/\text{m}$. These are a far cry from 10^{-29} to 10^{-36} !

Anspaugh et al. (1973), from Lawrence Livermore, examined the behavior of deposits from the cratering event "Schooner" and the accidental venting associated with the "Baneberry" event. They set up fairly elaborate sampling stations and followed the airborne radioactivity for six weeks after the Schooner event and for up to ten months after Baneberry. They came back after two years for a FIDLER survey (see chapter 14) of surface deposition. As much as half of the deposited debris was moved by the saltation process within twenty-four hours. The variation of air activity with time, after the Schooner shot, based on the activity of ^{181}W gave a half-life of thirty-eight days, quite similar to the figure for plutonium given by Wilson, Thomas, and Stannard. However, this covered only about 1,250 hr after the shot. For Baneberry, the half-life was seventy-six days based on data taken over a period of several months. There was considerable scatter of the points, however, as illustrated in figure 15.16A and B.

There were many other investigations of the trend of resuspension with time. In toto, these resulted in a formulation by Anspaugh, Shinn, and Wilson (1974) as follows:

$$K(t) = 10^{-4} \exp(-0.15 \text{ d}^{-1/2} \sqrt{t}) \text{ m}^{-1} + 10^{-9} \text{ m}^{-1}$$

where $K(t)$ is the resuspension factor in m^{-1} and t is the time since the contaminating event. The second term is introduced on the assumption that no further decrease occurs in the resuspension process after the level of 10^{-9} m^{-1} is reached.^(a)

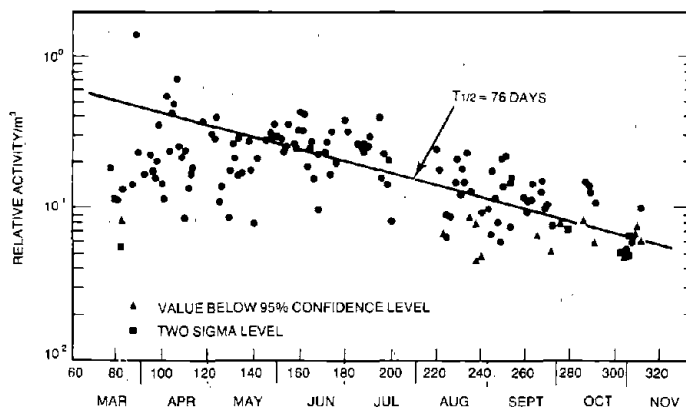
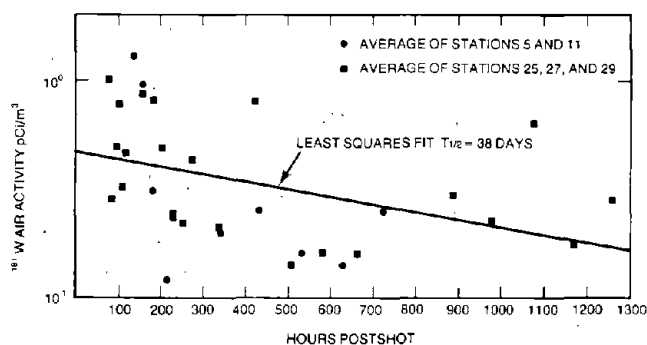
There were other views on the change of the resuspension factor with time. Healy (1984) takes the view that the data have so much scatter that no reliable value for a half-life can be derived. Indeed, there may be very little change in the availability of material for resuspension once the initial settling out processes are over.

(a) The constraints that underlie the formula are:

1. half-time for decrease in first ten weeks should approximate five weeks
2. this should about double over the next thirty weeks
3. the initial resuspension factor was 10^{-4} m^{-1} .

FIGURE 15.16A.

Tungsten-181 air activity as a function of time at the five downwind stations within six miles that were closest to the line of maximum deposition from Project Schooner. Data were normalized to the first sample taken after seventy hours had elapsed following the detonation. (Redrawn from Anspaugh et al. 1973.)

**FIGURE 15.16B.**

Gross gamma air activity levels as a function of time at Station 4 three to eleven months after the Baneberry venting. The solid line is a least-squares fit to the data points. (Redrawn from Anspaugh et al. 1973.)

Work on resuspension has continued with measurements at NTS and Rocky Flats and experimental field work, particularly at Hanford. Some of it involved nonradioactive tracers. The reports by Sehmel (1977, 1980a,b) from Battelle-Northwest include effects of vehicular, even pedestrian traffic, breakdowns into respirable and nonrespirable sizes, etc. The results were expressed as resuspension rates (fraction per second) rather than the resuspension factor, but they can be used for the same purposes. Nonrespirable particles had resuspension rates on the order of 10^{-11} per second. Resuspension rates for respirable particles ranged from 10^{-11} to 10^{-7} per second. There was a very slow weathering half-life for these stable substances on the order of many years. A photograph of the fairly elaborate equipment used for sampling at different heights in this Battelle work is given as figure 15.17.

Work in humid environments is not as plentiful. Milham and colleagues measured plutonium resuspension and calculated the resulting dose from agricultural operations (plowing, tractor movements, etc.) in an old field at the Savannah River plant (Milham et al. 1976). The plutonium had been deposited from global fallout and atmospheric releases from the plant. They calculated resuspension factors for agricultural operations of $103 \times 10^{-8} \text{ m}^{-1}$ at a distance of 7.8 m downwind, $5 \times 10^{-8} \text{ m}^{-1}$ at 30.5 m downwind, and $24 \times 10^{-8} \text{ m}^{-1}$ at the tractor location. McLendon et al. (1976), also from Savannah River, made many

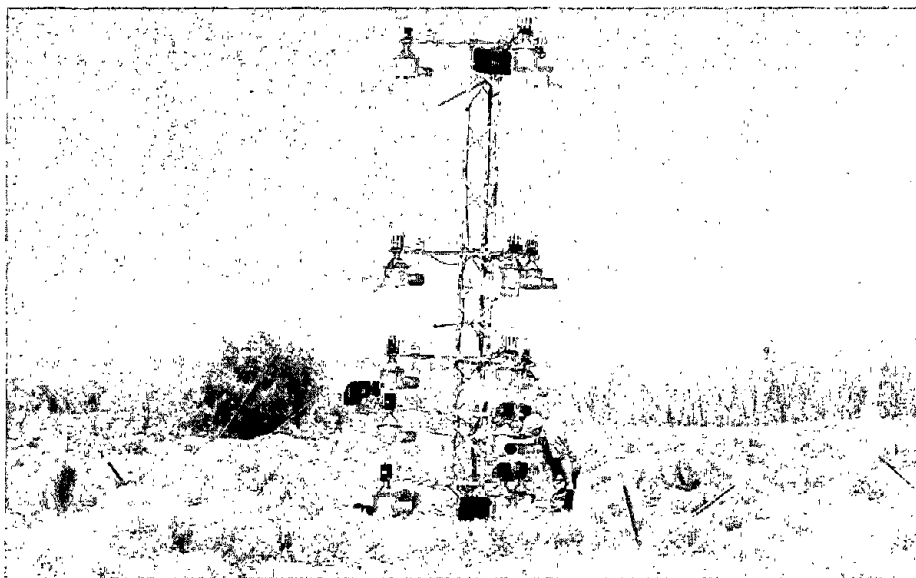


FIGURE 15.17. Measuring tracer resuspension by wind on the Hanford site. (From Sehmel 1977.)

measurements of concentration ratios for plutonium in soil and in animals, as well as uptake by plants. They also included concentrations in resuspendable material but did not calculate resuspension factors. Work at Oak Ridge has already been cited. While it is difficult to generalize, what information we have is consistent with the idea that resuspension factors will, in general, be lower in the humid southeast than in the west. However, there are many sandy areas in the east, beaches and dunes, and the chances of drought. Therefore, such a conclusion can have only general significance. For individual cases, it has been agreed that local measurements should be made whenever possible.

Despite all of the effort expended on measurements, the resuspension factor has never been entirely satisfactory for environmental situations. An obvious problem is that the numerator and denominator may have different origins. Since particles can be carried long distances by wind, the ambient air activity may, in fact frequently does, derive from soil at some distance from the point of measurement. This was made clear in the radionuclide field by some of the work from the safety shots at NTS (chapter 14). The potential lack of relationship between numerator and denominator should have been intuitively obvious, but it seemed to take many failures and much convincing to impress the problem on practicing health physicists who were anxious to have a way to predict hazard. Only when the source is large and well diffused in the environment is there a reasonable chance for measurements of surface contamination, using the resuspension factor, to be predictive.

3. Mass Loading

A different but not necessarily better approach is the so-called "mass-loading" approach. Whicker and Schultz remark on it as "perhaps the simplest." If it is

assumed that all the dust suspended in the airstream came from soil in the contaminated area, the following relation can be postulated:

$$X = MC_r$$

where

- X = air concentration in $\mu\text{Ci}/\text{m}^3$
- M = dust load of air in g/m^3
- C_r = concentration in the resuspendable fraction of the soil, in $\mu\text{Ci}/\text{g}$

M can be measured by air filters and has been a standard parameter in industrial hygiene for many years. For nonurban locations, it is about 9 to 79 $\mu\text{g}/\text{m}^3$ (mean 38), but under conditions of high winds over bare fields, it may reach as much as 1 to 10 mg of soil/ m^3 . For urban locations, it will be higher than the mean of 38 $\mu\text{g}/\text{m}^3$. The EPA uses 100 $\mu\text{g}/\text{m}^3$ for general purposes.

Estimation of C is more difficult. If the distribution of the contaminant is uniform with depth, soil samples can be sieved and the activity of different fractions measured. Frequently it is not uniform. Fresh deposits are seldom uniformly mixed, but may be confined initially to the top few millimeters of soil. This makes sampling and the problems of screening and sizing much more difficult.

The mass loading approach was given full treatment by the Los Alamos (Healy) and Lawrence Livermore (Anspaugh) people and was embraced by EPA in its draft guidance on dose limits for transuranium elements in the environment, which we will consider in a later section. It has been fairly generally agreed that the mass loading approach is not a good one for fresh deposits because of the lack of mixing with soil. However, for aged deposits, it may be useful. As described earlier, the Lawrence Livermore people set up a cascade impactor study in the GMX area of NTS and studied plutonium distribution in a seventeen-year-old deposit. Specific activity values, while not constant, did not vary greatly over the range of particle sizes measured (>7 to 0.01 to 1.1 μm), i.e., there was no obvious preferential association of plutonium with a particular particle size.

However, for fresher deposits (and this may include most of those of interest), there may be fractionation of plutonium and perhaps other radionuclides by particle size. Tamura, at Oak Ridge, whose work we met as part of the work of the NAEG (chapter 14) gave particulars for NTS, Rocky Flats, Mound Laboratory, and ORNL. Each had its own characteristic distribution of activity over the particle-size distribution (Tamura 1977). In the presence of appreciable selectivity among particle sizes, the mass loading concept cannot be applied without introducing correction factors for any skewing of the activity among the particle-size distributions.

The mass loading concept was tested by Anspaugh, Shinn, and Wilson (1974) and Anspaugh et al. (1975) by comparing measured and predicted air concentrations of a number of nuclides at several sites. The results, based upon work by a number of investigators, are shown in table 15.11.

Except for one hiatus near ground zero from one of the safety shots at NTS, the agreement between predicted and measured air concentrations is reasonably good, although the measured values seem to be lower in general. Healy (1984) comments that the mass loading approach is the only one that shows the effect of different climates on resuspension with some reliability.

TABLE 15.11. Comparison of Observed and Predicted Air Concentrations Based Upon a Single Mass Loading Model

Location	Nuclide	Air Concentration	
		Predicted ^(a)	Measured ^(b)
<i>GMX site, USAEC</i>			
<i>Nevada Test Site</i>			
NE, 1971-1972	²³⁹ Pu	7.2 x 10 ⁻³ pCi/m ³	6.6 x 10 ⁻³ pCi/m ³
GZ, 1972, 2 weeks	²³⁹ Pu	0.12 pCi/m ³	0.023 pCi/m ³
<i>Lawrence Livermore Laboratory</i>			
1971	²³⁸ U	150 pg/m ³	52 pg/m ³
1972	²³⁸ U	150 pg/m ³	100 pg/m ³
1973	²³⁸ U	150 pg/m ³	86 pg/m ³
1973	⁴⁰ K	10 ⁻³ pCi/m ³	9.8 x 10 ⁻⁴ pCi/m ³
<i>Argonne National Laboratory</i>			
1972	²³² Th	320 pg/m ³	240 pg/m ³
1972	Natural uranium	215 pg/m ³	170 pg/m ³
<i>Sutton, England</i>			
1967-1968	Natural uranium	110 pg/m ³	62 pg/m ³

^(a)Predicted value is equal to the soil concentration (activity/g) $\times 10^{-4}$ g/m³

^(b)Most values are annual averages.

Source: Modified from Anspaugh, Shinn, and Wilson 1974.

4. Resuspension Rate

A third approach to resuspension is the *resuspension rate*, described briefly in connection with the early work of Healy and Fuquay. This considers the amount of the radionuclide present on the ground that is resuspended *per unit of time* by wind or mechanical disturbance. It differs from the resuspension factor in being expressed as reciprocal time, e.g., day⁻¹. It can give the velocity of resuspension by multiplication by the ratio of activity per unit surface area and the activity per unit volume.

This approach seems to tie in most closely with the large amount of work done as early as the 1940s on wind erosion and the more theoretical aspects. Healy (1980) presents much of this background in a very detailed discussion, but could not conclude that this formulation represents the best formulation under all conditions.

5. Comment

There is still controversy over the method for calculating airborne hazards involving resuspension, but recent advances have indicated that definitive resolution may be possible soon. It does appear that the resuspension factor is the least likely to be the method of choice, despite the considerable attention lavished on it by the internal emitter establishment. Healy (1980) leans toward the resuspension rate as "our favorite method because of the capability of

integrating over a contaminated area using accepted dispersion and deposition parameters to provide concentration isopleths around the area." It is the preferred method when soil and meteorological parameters can be clearly defined. The mass loading approach gets the nod from Healy for generic studies (1984)^(a) and appears to impress the Lawrence Livermore people. It has some apparent problems, but they tend to compensate each other. The predictive success shown in table 15.11 is one reason for tempered confidence in this approach. Fortunately, meteorology, like all environmental science, is being advanced rapidly by the use of computers and modeling, which cannot help but advance soil erosion work, including resuspension by wind.

The recent series of reports by Sehmel (1981, 1983) regarding particle resuspensions and translocation on and around the Hanford site and Bikini Atoll indicate that there is much current interest in the subject. There were some experimental releases of plutonium (Sehmel 1981) to help explain some inconsistencies in the isotopic composition of some of the samples gathered on the Hanford site. Sehmel has also prepared two reviews (Sehmel 1980a,b), the first a summary of resuspension variables and a reiteration of the great uncertainty of predicting resuspension factors (range from 10^{-10} to $10^{-2}/m^{-1}$), the other specific to resuspension of transuranic elements. He also gave a full review at the DOE symposium on actinide environmental research.

C. Environmental and Population Standards^(b)

Despite considerable activity, there are only a few standards in force that can be regarded as true environmental standards in the sense that they include pathway analysis, transfer factors, and the like to at least some degree. Briefly they are:

1. Drinking Water
2. Effluents from Light-Water-Cooled Nuclear Reactors
3. Surface Contamination Standards
4. Standards for Soil Contamination
5. The Uranium Fuel Cycle
6. Transuranics in the Environment

We will take these up, in more or less chronological order, although there was considerable overlap.

1. Drinking Water

Early activities. Limits were placed on the radionuclide concentrations in air and water (maximum permissible concentrations—"MPCs") in the work place during the Manhattan Engineer District (MED) days (chapter 16). We have seen much of the applications to air in earlier chapters and earlier in this chapter. Little more needs to be added to them here. Although the limits for water were initially for water intake in the workplace and theoretically served this purpose for many years, it was soon apparent that the rigid health physics practices in the major installations severely restricted intake of contaminated water or food

(a) Remember that Healy also views with suspicion any conclusions regarding figures for the decrease of resuspension with time because of the scatter of the data.

(b) Remarks on the basis for population standards appear also in earlier sections and in chapter 16.

in the plants. The MED water limit began to have more general application, but it still was an occupational limit, not an environmental limit in the sense that it did not consider environmental pathways.

MPC values for water were included in the 1950s reports of both the NCRP and ICRP. In the 1959 reports of both organizations (chapter 16), limits for several hundred radionuclides in water were given. These were calculated from metabolic models and known behavior of each element to prevent doses to the critical organ from ever exceeding the then-extant maximum permissible exposure rate for occupational exposure. The ICRP report (Publication 2, p. 6) suggested that populations should receive one-tenth of the genetic dose or one-thirtieth of the somatic dose allowed for occupational exposure. The NCRP (Report No. 22, NBS Handbook 69, p. 6) recommended that the dose to persons in the neighborhood of controlled areas receive no more than one-tenth of the dose allowed to radiation workers and that this would generally entail control of the average concentrations in water (or air) for population exposure.

In his book on the Tri-Partite Conferences (chapter 16), L. S. Taylor introduces several documents, most of them prepared in the United Kingdom in the middle to late 1940s, that concerned radioactive contamination of drinking water (Taylor 1984, Appendices 3, 6) and the carcinogenic effects of ingested radioactive materials (Appendix 4). These were *ad hoc* calculations for specific radionuclides and are not reproduced here since the author did not see the documents until after this chapter was completed. Some of the values square well with those developed later by the more systematic approaches (chapter 16); others were very conservative indeed. Their importance for our present review is the fact that *population* standards for drinking water were considered four decades ago outside of the MED operations, partly in preparation for the postwar uses of radioactive materials. Thus, current activities are far from new, except that they concentrate less on manmade radionuclides.

When the FRC began to develop its Radiation Protection Guides, it included a recommendation for population exposure (one-tenth of the occupational levels); discussed the control of environmental radioactivity (Report No. 2, see chapters 12 and 16); and gave specific guidance for intake of ^{131}I , ^{226}Ra , and ^{89}Sr and ^{90}Sr for protection of individuals in the general population. These gave ranges for average daily intakes with the top of the middle range (Range II) corresponding to the agreed-upon dosages to the population (individual 0.5 rem/yr, or an average of 0.17 rem/yr). Despite inclusion of some detailed discussion of control of environmental radioactivity, the FRC cautioned:

Because of the wide difference in possible concentration values applying to different environmental media and depending upon specified circumstances, the Federal Radiation Council has not made any specific recommendations on such values. The responsible Federal Agencies should develop specific concentration values to apply to appropriate control actions as part of their operation criteria.
(FRC report No. 2, paragraph 1.28)(a)

It was two years before the most cognizant federal agency, the AEC, put forth specific concentration values—and these were not really tuned to specific environmental pathways, until the advent of Appendix I, as described in sections III E 3 and IV C 2 of this chapter.

(a) Much more detail of the operations of the FRC can be found in chapters 12 and 16.

The Code of Federal Regulations. Title 10 Part 20 of the Code of Federal Regulations gave two tables in its Appendix B. Table I contains concentration values for air and water for occupational exposure. Table II presents similar figures for offsite unrestricted areas. Fairly consistently, these were simply one thirtieth of the onsite occupational levels. Values were given for hundreds of radionuclides, much like the tables for occupational exposure in the ICRP-NCRP reports. Unlike the FRC's approach, which selected a few radionuclides to consider in depth, the approach in 10 CFR 20 was not specific for any given environmental pathway or set of circumstances. This lack of specificity is not surprising in view of the huge job facing the AEC and the fact that the environmental transfer phenomena reviewed in this chapter were poorly understood at the time. Thus, it cannot be said that Part 20 of Title 10 of the Code of Federal Regulations was truly responsive to the FRC's admonition quoted above. Only Appendix I in Part 50 was truly responsive, and this applied to only one type of installation, albeit an important one.

The provisions of Table II, Appendix B are still in effect for most of the hundreds of radionuclides involved, although some important ones have been selected out for individual treatment by the EPA, as we will see below, or by modifications in Regulatory Guides issued by the NRC.^(a)

The Base Broadens—Water Quality Criteria. As the extent of environmental contamination by chemical toxins and even infectious agents began to be generally appreciated, some broadly based activities began. They began in the states. For example, in the 1950s, the state of California produced a book of over five hundred pages (CAL 1952) that built upon years of earlier work throughout the world (see, e.g., Ellis 1937) concerning a large number of toxicants in water. This was expanded greatly under the California State Water Quality Control Board (McKee and Wolf 1963).

In 1966, the Secretary of the Department of the Interior sponsored a technical advisory committee to develop water quality criteria for a number of uses. These included domestic water supply, agricultural and industrial uses, toxicity of the contaminants to aquatic organisms, etc. The report (Water Quality Criteria 1968) became a basic reference for all agencies, local, state, and federal.

The organization of EPA in 1970 (see chapter 11 and 1972 amendments to the Water Pollution Control Act) transferred broad responsibilities for water quality to the new agency. Under a contract with the NAS-NRC and the National Academy of Engineering, a report giving broad criteria for water quality was produced (NAS-NRC 1972). This was followed by an extensive EPA compilation entitled "Quality Criteria for Water" (EPA 1976b). Criteria were spelled out for several uses and for a large number of chemicals and other potential pollutants.

These criteria did not include radionuclides, since these were still considered the domain of AEC and its successor agency ERDA.

The Safe Drinking Water Act of 1974—Interim Drinking Water Regulations. The above act gave the administrator of EPA authority over the quality of drinking water in public water systems and called for the speedy production of National Interim Drinking Water Regulations. Another contract was let and a report was

(a) A thorough revision of Title 10 of the Code of Federal Regulations is now in process by the NRC.

prepared by the NAS-NRC to set the pace. However, the proposed regulations were published by the EPA in the *Federal Register* well before the NAS-NRC report was issued. Those for microbiological and chemical contaminants were put out for discussion and comment on March 14, 1975 (EPA 1975b); those for natural and manmade radioactivity followed on August 14, 1975. It was proposed that they be incorporated in Part 40 CFR 141 and be effective at a suitable date after the NAS-NRC report had been issued and after a suitable period for public comment.^(a)

For naturally occurring radionuclides, attention was focused on ^{226}Ra and ^{228}Ra and gross alpha-particle activity (including ^{226}Ra). The proposed levels were:^(b)

Combined ^{226}Ra and ^{228}Ra	5 pCi/l
Gross alpha-particle activity (including ^{226}Ra)	15 pCi/l

For manmade radioactivity, the proposal suggested an annual concentration of beta-particle and photon activity in drinking water that would not produce an annual dose equivalent to total body or any internal organ greater than 4 mrem.

Calculations were given for the limiting annual concentrations that would produce this dose for only two nuclides. These were:

Tritium	Total body as critical organ	20,000 pCi/l
^{90}Sr	Bone marrow as critical organ	2 pCi/l

There was much discussion of the costs involved, for it seemed clear that many public water supplies (estimated then at about five hundred community water systems) did not meet the proposed radium standard. The necessary means for clean-up were discussed, including prominently the application of the ion exchange techniques used in water softeners.

The figures were based on estimates of risk using the linear no-threshold concept for dose-effect relationships (chapter 16). For the radium limit, the associated risk was estimated at 0.7 to 3 fatal cancers annually per million exposed persons. The corresponding risk estimates for the 4 mrem/yr proposed for manmade radiation were calculated as 0.4 to 2 cases per million exposed persons per year. The document also indicates that the 4 mrem/yr is not likely to be exceeded by sources currently in existence (deposited fallout radioactivity and effluents from other sources). There is no discussion of the validity of the choice of risk made in comparison to other risks of existence. Much more detail was given in an EPA document entitled *Statement of Basis and Purpose for the Proposed National Interim Primary Drinking-Water Regulations* dated August 15, 1975, but not numbered or otherwise identified. For written comments and a public hearing, the EPA requested, especially, further information on such things as number and location of public water supply systems that would be affected, the numbers that would require radium analysis, etc.

(a) EPA noted that the PHS limits then in use were enforceable only for interstate carriers of drinking water and for contaminants causing communicable diseases.

(b) Surface-water supplies ordinarily contain little radium. Thus, these limits for practical purposes applied primarily to ground-water supplies.

Reactions to these proposals were quite sharp. The Energy Research and Development Administration (see, for example, Gossick 1975) contended that present radiation standards for drinking water supplies were adequate. The average annual dose from natural background on the order of 130 mrem at sea level made the limitation of potable water to 4 mrem seem absurd to ERDA and the costs to many small communities out of proportion to the health effects prevented. There was a sizeable feud between the two federal agencies on this subject.

Robley Evans (chapter 1) addressed a strong letter that contained, briefly, the following points (Evans 1975):

1. There are many water supplies with ^{226}Ra values between 10 and 36 pCi/l. These supply a total population of over 30,000 persons in nineteen cities. Careful epidemiologic studies have revealed no deleterious (or beneficial) health effects in these populations.^(a) Furthermore, over 400,000 persons consume water with more than 4 pCi/l of ^{226}Ra , again with no demonstrable health effects.
2. The daily intake of water is more like 1 l/day than the 2 l used in the calculations.
3. Measured body burdens of radium in subjects existing under the current 30 pCi/l limit (see ICRP) are well below those associated with measurable effects, i.e., about 0.001 μCi versus the accepted limit (occupational) of 0.1 μCi .
4. The linear no-threshold relationship does not apply to radium in humans (see chapter 1 for Evans's many papers on this subject).
5. The retention of radium is not well represented by an exponential function of time. A power function (the Norris equation—see chapter 1) is considered a better description, and its use supports a higher MPC in water.
6. A quality factor (chapter 16) of 10 is too high for radium. It should be 3 (chapter 1).
7. No evidence is presented that indicates problems with the limits promulgated by ICRP, NCRP, and FRC.
8. Gross alpha measurements should be in counts per minute, not pCi.

There was more in the Evans letter, but the above is enough to present his arguments. Evans suggested that the supplies that currently run above 5 pCi Ra/l be given variances until the standards could be reconsidered, particularly since the economic costs were, in his view, inflationary.

In 1976, the EPA published "Drinking Water Regulations—Radionuclides" in the *Federal Register* (EPA 1976b).^(b) It reviewed the responses, made some changes in detail, but retained the maximum contamination levels as proposed, except that the calculated level for ^{90}Sr associated with 4 mrem/yr became 8 pCi/l rather than 2 pCi/l. The regulations went into effect on June 24, 1977.

(a) More detail on these supplies and the investigations are contained in chapter 1.

(b) In the next year, the NAS-NRC produced a set of recommendations to EPA under the title, *Drinking Water and Health* (NAS-NRC 1977).

There has continued to be opposition to the levels chosen and requests for reconsideration (e.g., Evans 1980), but, except for polite responses reiterating the EPA positions (e.g., Cothorn 1980), no substantive changes have occurred.

At the 1982 meeting of the Health Physics Society held at Las Vegas, Henry Lucas, from ANL and an old hand at the study of radium in drinking water, gave a paper on ^{226}Ra and ^{228}Ra in drinking water (Lucas 1982). He cited measurements from more than 90% of the communities in Illinois, Iowa, Missouri, and Wisconsin that obtained drinking water from wells that penetrate into deep sandstone aquifers and have relatively high radium contents. There were 117 communities with a total population of 1,442,000 that used water with ^{226}Ra concentration greater than 3 pCi/l and 91 communities with a population of 599,000 that regularly consumed water exceeding 5 pCi/l. He did not comment, as did Evans and as we saw in chapter 1, that no health effects had been found.^(a) He did comment on some anomalous variations in the ^{226}Ra - ^{228}Ra ratio that required further investigation.

The 1977 water standards specifically excluded radon and uranium. In 1981, EPA circulated a draft of "Suggested Action Guidance" (SAG)^(b) for uranium in drinking water (EPA 1981a). The level suggested was 10 pCi uranium per liter as an *upper limit* on the basis of radiation carcinogenesis and kidney damage. The radiotoxicity derivation used the ICRP Publication 30 model for uranium metabolism and EPA life table estimates of radiation effects. The postulated effect was based entirely on calculated dose. To date, there have been no cancers known to be associated with natural uranium except those described in animals at very high doses (chapter 2). For kidney toxicity, it was quoted that deleterious effects have been seen down to "dose rates" on the order of 0.1 mg/kg.

At the same Las Vegas meeting of the Health Physics Society mentioned above, two of EPA's principal workers with standards for radionuclides in water, William L. Lappenbusch and C. Richard Cothorn, enlarged upon the proposed criteria for uranium (Lappenbusch and Cothorn 1982).^(c) They stated that surface, ground, and domestic waters in the United States "seem to average 1, 3 and 2 pCi/l respectively of natural uranium." The Oak Ridge National Laboratory made some estimates for EPA of communities in this country that were above these averages. Some 64,000 community water supplies were measured. Of these, 25 to 650 exceed 20 pCi/l, 100 to 2,000 exceed 10 pCi/l, and 2,500 to 5,000 exceed 5 pCi/l. Lappenbusch and Cothorn proposed review of the implications of these facts vis-à-vis their proposed uranium standard at a national workshop for radioactivity in drinking water scheduled for late 1982. One was actually held in 1983 and is described briefly below.

In response to proposals for ground-water regulations in the state of New Mexico, Evans (1976b, 1981) referred to chapters 1 through 5 of the *Handbook of Experimental Pharmacology* edited by Hodge, Stannard, and Hursh (referenced in chapters 3, 9, 16, and elsewhere) and the 1975 Conference on Occupational Health Experience with uranium, also referenced earlier. The facts reemphasized that chemical toxicity of uranium should be the basis for control

(a) It is a moot question whether or not the search was sufficient or the populations were large enough to support an epidemiologic study.

(b) EPA-SAGs are not legally enforceable standards but advisories.

(c) The same meeting and same issue of *Health Physics* (Vol. 43, No. 1) contained several other papers regarding radionuclides in drinking water.

and that accepted levels for chemical toxicity are much higher than the 0.1 mg/kg quoted by EPA. The calculated water levels would be 1,200 pCi U/l using the EPA-SAG definition of the curie of uranium and the accepted level for threshold kidney damage (3 mg/kg).

The pot seems to still be boiling on water standards. The national workshop on radioactivity in drinking water was held under EPA auspices at Easton, Maryland, on May 24-26, 1983. It examined all aspects for radium, radon, and uranium in drinking water through seven specialty committees but limited itself to natural radioactivity. The proceedings of this workshop have appeared (Cothern and Lappenbusch 1985). It contains a full review of the EPA's activities and present position (Lappenbusch and Cothern 1985). What the final outcome will be regarding standards for drinking water can only be conjectured. The comprehensive paper by Wrenn et al. (1985) gives a new metabolic model for uranium and radium, and tentative limits of 100 $\mu\text{g/l}$ for uranium in drinking water. They also suggest relaxation by a factor of four for the radium limit.

2. Effluents from Light-Water-Cooled Nuclear Reactors

This was the earliest limit to include the vectors of food pathways as discussed earlier in this chapter (section III E 3).^(a) It is contained in Appendix I^(b) of the Code of Federal Regulations (10 CFR 50). It is still in force and is considered to have functioned very well in preventing any undue population exposures from this source in normal operations. The basic provisions of Appendix I are repeated below for the reader's convenience.^(c)

- a. The calculated annual total quantity of all radioactive material above background to be released to the atmosphere for each light-water-cooled nuclear power reactor should not result in an estimated air dose . . . in unrestricted areas in excess of 10 mrad of gamma radiation or 20 mrad of beta radiation.
- b. The Commission^(d) may specify as guidance on design objectives a lower quantity of radioactive material, e.g., annual external dose from gaseous effluents to any individual in an unrestricted area of not more than 5 mrem to the total body or 15 mrem to the skin.
- c. The calculated annual total quantity of all radioactive iodine and radioactive material in particulate form released from each light-water-cooled nuclear reactor shall not result in an annual dose or dose commitment from *all pathways of exposure* in excess of 15 mrem to any organ.
- d. The calculated annual total quantity of ^{131}I in gaseous effluents shall not exceed 1 Ci for each light-water-cooled nuclear power reactor at a given site.

These limits were originally set by the AEC and are now applied by the NRC, although the NRC is busy revising the applicable parts of the Code of Federal Regulations; and some details may be changed. It seems likely that the control by environmental pathways will continue to govern this segment of the nuclear power enterprise.

(a) Discussion of derivations was given there also.

(b) Note again that this is the letter I not a number.

(c) These were paraphrased from the Code of Federal Regulations.

(d) The NRC.

3. Surface Contamination Standards^(a)

We saw (chapter 14) that an important reason for the safety shots with plutonium, such as Test Group 57 and Operation Roller Coaster, in the late 1950s and early 1960s, was to test the validity of the rather arbitrary guidelines set up by the military in the event of a contaminating incident, e.g., a "Broken Arrow."^(b) For many years, the military had a fairly elaborate set of guidelines for denying or restricting access, or allowing regular living activities, etc., on the basis of radioactivity at the soil surface. Most of them were and are in procedural manuals and are classified, but some can be discussed.

In 1956, the Los Alamos people (Harris et al. 1956) suggested that an initial contamination level after the event of $100 \mu\text{g}/\text{m}^2$ ($6 \mu\text{Ci}/\text{m}^2$) of ^{239}Pu was realistic for lifetime occupancy. It will be recalled (chapter 14) that one of the objectives of Test Group 57 in Operation Plumbbob, in 1957, was to test the validity of this line and that contours for animal exposures were placed nominally at 10, 100, and $1,000 \mu\text{g}/\text{m}^2$. The results of this test could hardly be construed as validating or negating the validity of these levels. Yet, soon after publication of the reports from Test Group 57, and allegedly based on them, we find an emergency level of $1,000 \mu\text{g}/\text{m}^2$ being proposed as the line at which access to an area would be denied.^(c) This was in the classified literature for a while (Dick 1972, 1982; Boecker 1972),^(d) but saw fairly wide distribution later.

In 1958, the Air Force Special Weapons Center issued a technical note concerning aircraft accidents involving plutonium contamination (Baker, Boecker, and Dick 1958), which gives one standard for soil, $1,000 \mu\text{g}/\text{m}^2$ ($61 \mu\text{Ci}/\text{m}^2$), and one for air, $1,000 \text{ d}/\text{min}/\text{m}^3$. It gives procedures to use, areas potentially involved, etc., but no discussion of the basis for the limits. A bit more was contained in a report from the Test Group 57 work (Dick and Baker 1961).

In the same year, a manual was produced under the Defense Atomic Support Agency (DASA 1961) that gives time of occupancy factors for areas contaminated to different levels and also permissible surface contamination levels for conditions producing different resuspension factors. Lifetime occupancy was considered compatible with initial^(e) ground concentrations of ^{239}Pu of $1,000 \mu\text{g}/\text{m}^2$ or less, an indeterminate period when it was $3,000 \mu\text{g}/\text{m}^2$, 8 days when it was $4,000 \mu\text{g}/\text{m}^2$, and 3.6 days at $5,000 \mu\text{g}/\text{m}^2$. The derivation of these figures is not given, except it appears that a resuspension factor of $10^{-6}/\text{m}$ was employed.

The permissible surface levels at different resuspension factors were calculated as shown in table 15.12.^(f)

- (a) This discussion refers entirely to surfaces in the environment, not interior surfaces that are regulated to much lower levels. Also, it is limited to plutonium, since that is where the emphasis has been placed. Levels for a few other substances were considered, but they are not numerous.
- (b) Nonnuclear detonation involving the crash of an aircraft carrying a nuclear weapon.
- (c) This is, of course, not the same operation as allowing lifetime exposures as proposed for the $100 \mu\text{g}/\text{m}^2$ line. It was an emergency level.
- (d) I am greatly indebted to these former Air Force officers for personal communications and copies of unclassified reports on this subject.
- (e) Remember that these levels referred to a single event and to the initial contamination.
- (f) The reproduction of this and other figures from military documents should be regarded as illustrative only, primarily to show what was done. The standards actually used tended to be site-specific, and details have been revised many times since the work quoted above was done.

TABLE 15.12. Maximum Initial Surface Contamination Levels Under Various Conditions

Conditions of Dust Production (dry surface)	Resuspension Factor	Permissible Surface Contamination ($\mu\text{g}/\text{m}^2$) ^(a)
Vehicular traffic (Nevada)	7×10^{-5}	10
People working or active in a closed area	4×10^{-5}	20
Dirty rural, suburban, and metropolitan atmosphere	7×10^{-6}	100
People working or active in an open area	2×10^{-6}	360
Isolated area where basically only relatively low-velocity wind is the resuspending force and people are taking great care to prevent resuspension	$\sim 7 \times 10^{-7}$	1000 (100 dpm/m ³)

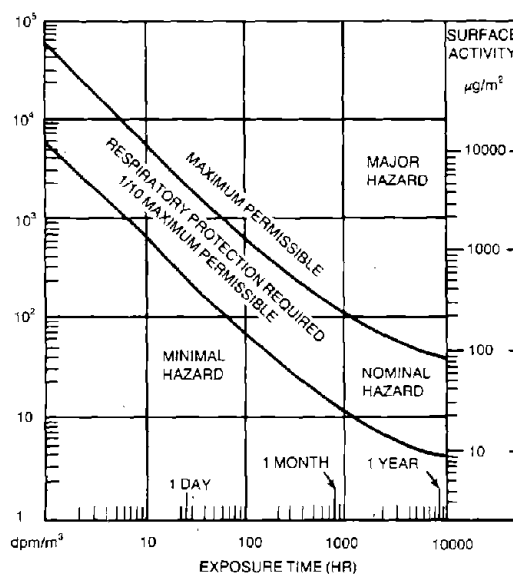
(a) As plutonium.

Source: Modified from Report LA-2079 via DASA 1961 (see footnote f, p. 1343).

In view of the evanescent nature of the resuspension factor and its questionable validity, it is unlikely that these recommendations were applied very conscientiously. Indeed, especially since these are applications for emergency conditions, there has been a tendency to assume some single "reasonable" level for resuspension and apply a single set of controls.

Probably the most ambitious undertaking in this manual was a graph relating exposure time to surface activity in $\mu\text{g}/\text{m}^2$ or dpm/m³. This is reproduced as figure 15.18.

FIGURE 15.18. Airborne plutonium contamination hazard estimated from surface activity (dry), assuming a resuspension factor of 4×10^{-6} . (Redrawn from a DASA manual [DASA 1961] that brought it over from some general procedures for Special Weapons Accidents [see footnote f, page 1343].)



It is not clear to what extent such a graph was ever used, except for planning. However, it is interesting in its demarcation of "major," "nominal," and "minimal" hazard and also by requiring respiratory protection along a line at one-tenth of the maximum permissible limit.

In 1968, Kathren of Battelle-Northwest, produced a general review of the status of surface contamination levels for environmental plutonium (Kathren 1968). This is quite complete on the environmental behavior of plutonium, in its review of the several recommendations extant, and in derivation of acceptable interim standards. Indeed, it raised some eyebrows by bringing into the open literature some regulations that, while no longer classified for security purposes, had not received much general distribution. He also uncovered confusion and inconsistencies by listing maximum permissible alpha contamination standards for the workplace in many countries around the world and some of the environmental levels in use. These include U.K. figures of $0.1 \mu\text{Ci}/\text{m}^2$ for "inactive" areas and $1 \mu\text{Ci}/\text{m}^2$ for "active" areas, the U.S. Department of Defense (DoD) level of $62 \mu\text{Ci}/\text{m}^2$ ($1,000 \mu\text{g}/\text{m}^2$), and Navy Publications (from the NRDL) that give $0.04 \mu\text{Ci}/\text{m}^2$ for unrestricted release (Sulit, Leahy, and Baietti 1961), and other Navy publications suggesting $0.62 \mu\text{Ci}/\text{m}^2$ for shipboard occupancy on a continuous basis (Schwab 1958; Leahy and Smith 1958).

Kathren calculated his own maximum permissible surface contamination levels for environmental plutonium. These were based on an allowable dose of 1.5 rem/yr to lung or pulmonary lymph nodes (approximately $3.2 \times 10^{-5} \mu\text{Ci}$ in pulmonary lymph nodes).^(a) The calculated values are given in table 15.13.

TABLE 15.13. Interim Maximum Permissible Surface Contamination Levels for Environmental PuO_2

	Average	Maximum
Urban, suburban, and recreation areas	10^3 dis/min per 100 cm^2 ($0.04 \mu\text{Ci}/\text{m}^2$)	10^4 dis/min per 100 cm^2 ($0.4 \mu\text{Ci}/\text{m}^2$), spread over $\leq 10\%$ of the total area included
Rural: truck farming, annual food crops, grazing land, milk-shed, etc.	10^4 dis/min per 100 cm^2 ($0.4 \mu\text{Ci}/\text{m}^2$)	
Rural: deep root perennials (e.g., nuts, certain fruits)	10^5 dis/min per 100 cm^2 ($4 \mu\text{Ci}/\text{m}^2$)	
Remote or Controlled: desert, forest, fenced or limited access areas	10^6 dis/min per 100 cm^2 ($40 \mu\text{Ci}/\text{m}^2$)	

Source: Modified slightly and reset from Kathren 1968.

For these calculations, Kathren used an air concentration half-life of 45 days (see above); a resuspension factor of 10^{-4} m^{-1} ; a particle size distribution of $2 \mu\text{m}$ mass median diameter with $\sigma_g = 1.5$; 20% deposition in the pulmonary compartment with 15% of this going to pulmonary lymph nodes; transfer half-life from lung to lymph nodes of 360 days; and a mass of 20 g for the pulmonary lymph nodes.

(a) Praise be, the entire derivation is given!

Obviously, these figures are more conservative than those used at the time by the military^(a) and are in line with ICRP-NCRP conventions, except for the use of pulmonary lymph nodes as "critical organ." Again it is doubtful if such a spread, i.e., $0.04 \mu\text{Ci}/\text{m}^2$ to $40 \mu\text{Ci}/\text{m}^2$ would be applied operationally instead of a single limit, but it gives flexibility if it is needed. This author finds no records of these limits having been adopted, as such, for use by the military or the regulators.

A comprehensive consideration of plutonium surface contamination levels for DoD action appeared in 1972 (DASA 1972). This report, seen only in draft form and classified "Official Use Only," presents the entire story again. It points out that all federal guidelines (i.e., DoD/AEC [Weapons Accident], U.S. Army, U.S. Navy, and U.S. Air Force) except AEC, use $1,000 \mu\text{g}/\text{m}^2$. No AEC limits for environmental decontamination had then been stipulated per se, but DASA inferred from parts of 10 CFR that they would be $5.6 \mu\text{g}/\text{m}^2$ as derived from indemnity agreements and $0.96 \mu\text{g}/\text{m}^2$ on the basis of permitted effluent releases to controlled areas and application of a resuspension factor of 10^{-6} m^{-1} .^(b)

After much discussion, the DASA report suggested three levels, each an order of magnitude apart, à la Test Group 57. These ranged from $50 \mu\text{g}/\text{m}^2$ for residences and urban areas; through $500 \mu\text{g}/\text{m}^2$ for rural farmland, grazing land, etc.; to $5,000 \mu\text{g}/\text{m}^2$ for remote, limited access or controlled areas. No derivations are given, although the lifetime organ doses are given for several organs at eight different levels. The maximum is 34 rad to the lymphatic system at $5,000 \mu\text{g}/\text{m}^2$ and the minimum 0.001 rad to bone at $5 \mu\text{g}/\text{m}^2$.

A personal communication from DASA, received while the above was still in draft form, indicated that the final version would present only one recommended level for action and that this would be $50 \mu\text{g}/\text{m}^2$. It has not been possible to determine whether or not this much more conservative figure has come into general use in the DoD.

Throughout these discussions, the proper choice of resuspension factor comes up for discussion. The consensus seems to settle on 10^{-6} m^{-1} for generic and most other uses. Fortunately, except for Palomares and Thule and a few unpublicized incidents, there has been little need to apply these ground contamination criteria. It is clear that some of the transfer factors under discussion in this chapter played a role in their derivation, but details, except for the Kathren work, are hard to come by.

4. Standards for Soil Contamination

The need for clean-up of former sites of radium, uranium, and related extraction and refining operations stimulated much work on the development of criteria for such enterprises. In chapter 11, we reviewed activities of the Oak Ridge Environmental and Health Physics groups in surveying over one hundred sites and helping to orchestrate their clean-up. As noted there, some of the sites were quite old and had long since been turned back to the public domain. Others were quite new in the sense that contaminated soil had been used for construction, etc.

(a) Because of the differing assumptions used, the relative doses cannot be calculated directly, but obviously only the highest level, $40 \mu\text{Ci}/\text{m}^2$ approaches the $62 \mu\text{Ci}/\text{m}^2$ used by the military.

(b) Allowable surface contamination levels for transportation are considerably lower.

A good statement of the problem and potential solution appeared in the EPA's preamble to its generation of standards for 40 CFR Part 192 (FR 1980a) and is quoted below:

Lands and buildings contaminated with uranium mill tailings pose risks to public health. The greatest hazard from tailings on open land is increased levels of radon decay products in buildings. When radon decay products are inhaled, they increase the chance of lung cancer. Exposure to direct gamma radiation and contamination of drinking water and food may also occur.

Tailings usually only pose significant risk to people who are exposed for a long time. However, some homes and other buildings have been found in which the radon decay product concentration is quite dangerous. There are such buildings, for example, in Salt Lake City, and in Canonsburg, Pennsylvania. Several buildings in Salt Lake City are immediately adjacent to a tailings pile, or have tailings in, under, or around them. In some of these, indoor radon decay product concentrations exceed the average occupational concentration limit for uranium miners (0.3 WL). Included among these is a fire station in Salt Lake City, where substantially elevated levels have been measured even when mechanical ventilation is used. In Canonsburg, an industrial park is now located on an inactive processing site. Eight buildings leased to commercial tenants are located directly over heavily contaminated land. Measurements during working hours show that all buildings have substantially elevated indoor radon decay product concentrations, with the highest average daytime level being 0.4 WL. These levels are dangerous and will continue. To allow DOE to begin remedial action under Pub. L. 95-604 to alleviate these hazards, we have decided to promulgate these immediately effective interim cleanup standards.

Studies of indoor background radioactivity in Grand Junction (Colorado), New York State, and New Jersey show that at least 10 per cent of houses with basements exceeded the interim standard's remedial action level of 0.015 WL. Because of this, we believe it would often be impossible to try to reduce levels for houses affected by tailings significantly below 0.015 WL by removing the tailings. Thus, it is unlikely that the final standards will be set at a level significantly more stringent than the interim action level of 0.015 WL, and remedial actions performed under the interim standard will not have to be redone. Furthermore, although we have not formally solicited public comments on the interim standards, the Nuclear Regulatory Commission and the Department of Energy have been consulted. For these reasons, we believe issuing immediately effective interim cleanup standards is justified.

Obviously, the story started long before this. While Oak Ridge was involved deeply with the operations,^(a) it was Los Alamos that was most consistently involved with the criteria and standards. As early as 1971, Jack Healy prepared a Los Alamos report on decision levels for surface contamination (Healy 1971). This did not particularly concern the general environment. It considered dose to the skin and possible inhalation or ingestion of material deposited on skin or clothing or in the home and possible transfer by resuspension. Over 180 isotopes were considered. It may well be that this research stimulated Healy's interest in general environmental contamination (or the interest may have already been present). In any event, he continued in the field and is still at it, as we saw in the previous section. In 1972, Healy circulated, within Los Alamos, a draft document for a plutonium-in-soils standard that set the pattern for his later work. By 1974, he proposed an interim standard for plutonium-in-soils (Healy 1974). He reviewed skin absorption, ingestion, inhalation, resuspension, contamination of clothing and of dwellings, and suggested provisional upper

(a) The surveys of previously utilized sites, mill tailings, etc.

limits for soil contamination.^(a) He derived the standards from extant recommendations for body burden and annual dose limits for population groups and individuals (ICRP 1966).^(b) This implied a maximum body burden of $0.004 \mu\text{Ci}$ of ^{239}Pu and a maximum lung burden of $0.0016 \mu\text{Ci}$. He also applied the Radiation Protection Guides of the FRC (chapter 16) and their ideas for Protective Action Guides. Healy reviewed the problems of applying soil limits based on amounts per unit surface area as was done for the limits described in the previous section, particularly the uncertainties in the depth of the soil layer to be sampled or considered significant. As a result, he presented his calculations on the basis of either the concentration in soil or the quantity per unit of surface area. Standards were thus derived that could be used on either basis. The operators could determine which to use according to the information they had available and what they felt most comfortable with.

After thorough consideration of each entry route and each step from soil to lung, including intake factors, Healy suggested interim standards for plutonium in soils as shown in table 15.14.

TABLE 15.14. Recommended Interim Standards for Plutonium in Soils

	In <100 μm Particle Size Fraction			Total**		
	D/M per g	$\mu\text{Ci/g}$	$\mu\text{Ci/m}^2$	D/M per g	$\mu\text{Ci/g}$	$\mu\text{Ci/m}^2$
Top 0.1 cm*	500	2×10^{-4}	0.4	1000	4×10^{-4}	0.8
Any one cm layer	500	2×10^{-4}	4	10000	4×10^{-4}	8

*For bare soil or areas with sparse vegetation. Where area is reasonably well vegetated (greater than 50% of the area is covered with low vegetation) and a reasonable root mat exists to hold the soil, the concentration listed can be applied to a 0.5 cm layer which would permit up to $2 \mu\text{Ci/m}^2$ in this layer.

**With the provision that the fraction with the particle sizes less than $100 \mu\text{m}$ is known not to exceed the limits given. If this is not known, the values for the $<100 \mu\text{m}$ fraction should be applied to the total.

Source: Reset from Healy 1974.

Note that the table gives not only both concentration and surface area bases, but the numbers are divided into two fractions according to the particle size measurements. The fraction larger than $100 \mu\text{m}$ was arbitrarily chosen as supporting a limit exactly equal to that below $100 \mu\text{m}$, and the total was thus twice that associated with the lower range. Limiting soil concentrations were also given for casual and deliberate^(c) ingestion, skin absorption, and several varieties of inhalation exposure.

(a) The lower limits were based on the ALARA principle.

(b) For details see chapter 16 and the review by Langham and Healy (1973). The body and lung burden figure is one-tenth of the limit for workers.

(c) This means "pica," the deliberate ingestion of dirt by children at play and is pegged a factor of ten lower because of the possibly greater absorption of plutonium from the gut in the very young and their potentially greater radiosensitivity.

Still later, Healy prepared a draft report examining the pathways from soil to man for plutonium (Healy 1976a). This was published as a Los Alamos report (Healy 1976b) and in an NAEG report in 1977 (Healy 1977). Pica in children and mechanical resuspension were more limiting than wind resuspension. Also, ingestion of foodstuffs containing plutonium could become an important pathway if all of the food was produced in the contaminated area, a fairly unlikely situation for most environments currently contaminated with plutonium.

In 1979–1980, the field broadened from plutonium to radium, uranium, other transuranics, and other relatively long-lived radionuclides such as ^{90}Sr and ^{137}Cs . In 1979, Healy and colleagues prepared a Los Alamos report entitled *Interim Soil Limits for D&D Projects* (Healy, Rodgers, and Wienke 1979). The suggestions were considered as tentative and preliminary partly because the expense of the clean-up operations could mount rapidly with relatively small decreases in the level to be aimed at. Also, a dilemma was posed in preparing these because the EPA was developing its proposed guidance for transuranium elements in the environment, to be discussed in the next section. They were suggesting limits based on doses of 1 mrad/yr to lung and 3 mrad/yr to bone for the alpha particles of transuranium nuclides. By contrast, the extant FRC guidelines were 0.5 rem/yr.^(a) Healy chose to utilize the latter since the EPA proposals were still in the review stage. The difference in clean-up levels is substantial.

The recommended soil limits in the Los Alamos report were as shown in table 15.15. Details of the many choices made are given in the text of the report. Note that a preliminary radium standard is cited. This is referenced in the bibliography for this chapter (viz., Healy and Rodgers 1978).

TABLE 15.15. Recommended Soil Limits^{a,b} (In pCi/g)

	Inhalation	Ingestion		External Radiation	All Pathways ^c
		Home Gardener	Full Diet		
^{231}Pa	50	740	150	250	40
^{227}Ac	2,000	4,900	1,000	300	250
^{232}Th	45	670	140	40	20
^{228}Th	1,000	37,000	7,800	55	50
^{230}Th (No Daught.)	300	4,400	940	36,000	280
^{238}U – ^{234}U	750	44	8	6,000	40
^{90}Sr	2×10^6	100	19	—	100
^{137}Cs	7×10^6	800	1	90	80

^aSoil limits for ^{241}Am and $^{239,240}\text{Pu}$ are available from EPA recommendations, and a soil limit for ^{226}Ra has been reported by Healy and Rodgers.

^bLimits are to apply to only one nuclide present in the soil. If more than one is present a weighted average should apply.

^cBased on diet of a home gardener.

Source: Reset from Healy, Rodgers, and Wienke 1979.

(a) Note rem, not rad.

Naturally, these Los Alamos standards were unofficial since they had not been through the *Federal Register* or other approval processes. Yet, they appear to have been used, informally at least for some clean-up operations. They are still under consideration by organizations such as the NCRP.

An important aspect of these and other soil standards is the choice of factor for gastrointestinal tract absorption. As we have already seen, there has been a tendency to apply larger absorption factors to very low-level long-term intakes, than to figures used for occupational exposures. Thus, Healy used a gastrointestinal absorption factor of 20% (0.2) for uranium instead of the 0.05 for water soluble forms (valence + 6) or 0.002 for insoluble salts (valence + 4) used for calculation of occupational standards. Such a change could, of course, make a significant difference (and did) in the criteria for clean-up. Healy prepared an informal survey of all the data on absorption of transuranium elements from the gastrointestinal tract as an appendix to another Los Alamos report (LA-UR-79-100 Excerpt) to document the choice of absorption figures and also circulated the compilation.

By this time, the EPA was assuming a central role. Fortified by provisions of the Atomic Energy Act and the Presidential Reorganization Plan No. 3 of December 1970, the agency proposed standards for plutonium in soils and for the clean-up of both older plant sites such as those described in chapter 11 and above, and for uranium mill tailings.

The formal development of general federal standards for plutonium in soils began in 1974 with an announcement in the *Federal Register* followed in 1976 by enormous documents entitled *Draft of Federal Guidance for the Environmental Limits of Plutonium Contamination in Soils*. These documents cited incidents of old and new contamination, criteria for derivation of risk, sampling and analysis methods, and anticipated impacts in addition to the proposed regulations. In line with the trend of the times to base limits on estimates of risk, the agency took the view that total risk should not exceed 10^{-4} to 10^{-5} /yr. They also took the view that no single activity should be permitted to contribute more than one one-hundredth to one one-thousandth of the basic radiation protection guide. For lung, with a proposed general population limit of 1.5 rem/yr, the allowance for an individual would thus be 2 to 15 mrem/yr, which equated to a risk of 10^{-6} to 10^{-7} /yr. They chose 10^{-6} for the most exposed individual.^(a)

The actual proposed limit for plutonium contamination in soils was based upon inhalation of suspended soil particles. It came out, after many tortuous calculations and sets of assumptions, to 25 dpm/g of soil for a sample constituting a 1-cm depth, or $0.2 \mu\text{Ci}/\text{m}^2$. The agency went to considerable pains to point out that the proposal was limited to contaminated soils, was not concerned with release limits from facilities, nor was it intended to supersede existing radiation protection guides. It was intended "only to supplement existing guides by specifying limits for one single source of activity from one group of radionuclides within broader limits." The equating of the soil concentration to lung dose was far too complex to be reproduced here. Suffice it to say that several new factors were introduced, such as an "Area Concentration Factor," and an "Enrichment Factor," and others, as well as choices regarding resuspension factors (or mass loading), etc.

(a) This is equated in one section of the report to 15 mrem/yr to the lung, but the final guidance gives 10 mrem as the maximum individual dose from this source.

One needs only to look at the final figures to expect that these tentative proposals would generate much opposition. The basic methodology was considered an advance by many, but the solidity of many of the "constants" that had to be cranked in was seriously doubted. The review process took many months. The ideas returned later in two forms—limits for clean-up of sites and a more general document on environmental radiation protection for normal operations of the uranium fuel cycle. We will review the latter in the next section. The clean-up standards took off in a slightly different direction. While they were concerned with radium and the actinides, they focused more on the risks of lung cancer from radon decay products and of fatal cancer from whole-body exposure to external gamma radiation. Indeed, it was the mill tailings issue that they aimed at most vigorously. The standards were described in the *Federal Register* in April 1980 (FR 1980a,b) and were to be implemented as part of the Code of Federal Regulations (40 CFR 192). This took place on September 30, 1983, as 40 CFR 192, parts D and E.

The figures, couched in terms of levels at which remedial action must begin, were as follows:

1. Average concentration of ^{226}Ra attributable to residual radioactive material from any designated processing site in any 5-cm thickness of soils or other materials within one foot of the surface, or in any 15-cm thickness below one foot, shall not exceed 5 pCi/g.
2. The levels of activity in any occupied or occupiable building shall not exceed an annual average indoor radon daughter product concentration of 0.015 Working Levels, including background, or an indoor gamma radiation rate of 0.02 milliroentgen per hour above background.

Note that these are for inactive sites. While EPA proposes the standards, DOE has the job and expense of clean-up. Currently, active sites are governed by the fuel cycle standards we will consider in the next section. Specific guidance for them is reported to be in preparation.

Many view these limits as too low and as putting an unnecessary burden on those who must pay for the clean-up.^(a) EPA appears to take the view that its environmental standards must be low since they cover only one pathway at a time, i.e., only a portion of the total risk to an individual in the population or an average for the population.

5. The Uranium Fuel Cycle

This is a long story and one we have not considered in any depth heretofore. Therefore, we must review it here. The standards are contained in 40 CFR 190 and were approved in two parts. Part A, which was proposed to go into effect on December 1, 1979, gives a blanket limit of 25 mrem/yr to whole body or any individual organ, except thyroid, which was allowed 75 mrem/yr. Part B concerned the total quantities of radioactive materials allowed to enter the general environment per gigawatt of electrical energy generated. These were:

1. less than 50 Ci of ^{85}Kr
2. less than 5 Ci of ^{129}I
3. less than 0.5 Ci of ^{239}Pu and other alpha-emitting transuranium radionuclides with half-lives greater than one year.

(a) There were also many questions of scientific basis and derivations.

The effective date for ^{85}Kr and ^{129}I was proposed to be January 1, 1983, to give time for the industry to install equipment and devise mechanisms for meeting these criteria. The guidance was addressed to federal agencies.

Note that these standards were expected to apply to all operations within the uranium fuel cycle. Thus, like the estimates of dose from the uranium fuel cycle, discussed earlier, they apply to milling, conversion, enrichment, fuel fabrication, light-water-cooled reactors, fuel reprocessing, and transportation of radioactive materials in connection with any of these operations. The standards were calculated to reduce the total potential health impacts, i.e., cases of cancer, leukemia, and serious genetic effects in human populations by one thousand or more.

Obviously, monitoring operations as extensive and diversified as those named above and measures to insure that neither the broad limits of radiation dose nor the maximum permissible releases were exceeded posed a Herculean task that was not shouldered without protest. The history is capsulized below.

In May 1975, the Office of Radiation Programs of EPA circulated a draft environmental statement outlining the proposed radiation protection requirements for normal operations of the uranium fuel cycle (EPA 1975a). They were as stated above. Hearings in the ensuing months brought general but not unanimous approval of the approach taken as a first attempt to establish an ALARA approach to standards across the entire fuel cycle. There was, however, widespread criticism of the methods and validity of the data used to support the figures and the lack of involvement of a large number of informed agencies and individuals in the development of so broad a set of regulations. There were many (e.g., Parker 1976) who advocated a national effort to bring the "best collective judgement" to bear, to obtain a true consensus on evidence of health effects at low levels of radiation and "orderly prediction of when human data can be expected to yield positive results that can be tested against health effects postulates."

There were others (e.g., Evans 1976a; Taylor 1976; Liverman 1975, 1976; Mattson 1976) who took, in various forms and to various degrees, the view that current standards were functioning well, measurements in the environment at such low levels would be almost impossible to make and at best would be subject to large errors because they were at or near the limits of measurements, and that embracing the linear no-threshold formulation for dose-response was unacceptable for assessments of this kind.^(a)

Few of the objections involved specifics of pathway analysis, although many considered that it could not be done. We must pass by the details of many responses since they are beyond the purview of this chapter and bear more on the philosophy of standard-setting than on environmental transport.

It is obvious that there is room for legitimate differences of scientific opinion and judgment in this complex area. The broad fact remains that a fully national or preferably international consensus has never been aimed at, nor have suitable mechanisms been proposed to arrive at same.^(b) Thus, the guidance promulgated by EPA, in this area, stands as legally legitimate but seriously

(a) Note it was largely assessment that they were criticizing.

(b) The EPA may have taken the view that such a gathering could do nothing but agree to disagree. Also, the EPA was under pressure to produce radiation standards for the environment.

questioned on the grounds of the scientific basis for many of the derivations and the methodology and judgmental factors, including the wisdom of the fractionated approach.

The problems raised did not seem to be enough to force major changes, and the proposed limits went into effect under 40 CFR 190 as of the proposed dates. It is the NRC that has had the major burden of implementation. There have been a series of "Regulatory Guides" that incorporate or concentrate on implementation of 40 CFR 190 as well as 40 CFR 192.

6. Transuranium Elements in the General Environment

In 1976, the Nevada operations office of ERDA held a symposium at Gatlinburg, Tennessee, on the subject "Transuranics in Natural Environments." The report from this can be regarded as the beginning of a marked crescendo in interest in transuranic elements in the general environment. In 1977, EPA came out with yet another new document, which contained similar yet somewhat different proposals from those for the uranium fuel cycle. It was entitled *Proposed Guidance on Dose Limits for Persons Exposed to Transuranic Elements in the General Environment* (EPA 1977a) and was to cover all important pathways of the transuranic elements to humans. It suggested, as indicated earlier, limiting dose rates from exposure to transuranium elements in the general environment to 1 mrad/yr to the pulmonary lung or 3 mrad/yr to the bone; it stated that the recommendations be used only for guidance or possible remedial actions and not for limits on planned releases; and it suggested that implementation be on a site-specific basis. To facilitate implementation, they suggested that a soil contamination level of $0.2 \mu\text{Ci}/\text{m}^2$ for samples collected at the surface to a depth of 1 cm and below a stated particle size^(a) would establish "a reasonable screening level." A derived air concentration based on activity median aerodynamic diameter (AMAD) not exceeding $0.1 \mu\text{m}$ would be $1 \text{ fCi}/\text{m}^3$ for alpha-emitting transuranics. This constituted a screening level for the air.

There was considerable discussion of the risks associated with these levels. They were less than one chance in a million per year and less than ten chances per hundred thousand in a lifetime for development of cancer from continuous exposure at the stated dose rates. The fact that the guidance was aimed at the small fraction of the total population at greatest risk was also emphasized. There were illustrations of what the impact (or lack of it) would be at some of the sites known to be contaminated with transuranics (Rocky Flats, Mound Laboratory, NTS, and Trinity site). Finally, it was again emphasized that the guidance was not intended to supersede existing overall radiation protection guides.

It was proposed that agencies implementing the guidance be required to estimate dose rates to persons from measured air and/or soil concentration levels. It was stated that nearly all land outside the boundaries of existing contaminated sites in the United States is probably below the levels specified in the guidance, and little or no remedial action would be required.

This large volume, despite its caveats, brought another large volume of comments and criticisms. Many of them (e.g., ERDA, undated) were along the same lines as those in 1975–1976 for the uranium fuel cycle, e.g., the basic philosophy

(a) The report states a particle size "under 1 mm," but this author is not sure that that is what was meant.

used for standard setting, the linear no-threshold hypothesis, one area being selected out for attention, etc. Much must again be omitted since it does not bear directly on environmental considerations. Yet, it must be noted that the new numbers introduce very substantial burdens of implementation and enforcement—out of proportion in the opinion of many of those commenting—to the number of health effects prevented.

On the environmental side, there was heavy criticism of EPA's choice of the mass-loading approach to resuspension. This approach, as we saw earlier, involves the assumption that all airborne particles have their origin in the locally contaminated soil. As stated earlier, EPA introduced an "Area Correction Factor," which could be employed when the source area was small and perhaps did not contribute all of the measured activity in the air, but this was not considered sufficient.^(a)

In response to these and hundreds of other comments, the EPA produced a Response to Comments (EPA 1978b) and a revised text of the guidance. Basically the agency concluded that the comments did not raise substantive new issues and that the basic guidelines would remain. There were changes in detail and much rebuttal of the comments.

These proposals remain in a "draft" stage, although promulgated informally in the *Federal Register* (42 FR 60956, November 30, 1977).^(b)

7. Commentary

This review of standards applicable to the environment is cursory. It necessarily omits many pertinent arguments and discussions primarily because many of them have little to do with the environmental aspects of the design and justification for the standards. Some of the ideas can be found in other chapters. Even this cursory review, however, makes it clear that recent efforts have been fraught with controversy. The reasons are numerous.

1. Few of the recent statements give clear-cut derivations of the figures, especially the justification for judgments made.^(c) Those that do frequently have been criticized as lacking clear scientific grounds for acceptance.
2. The idea of separating off a particular radionuclide and a segment of the environment and applying a very low limit because it is only part of the total exposure has been difficult for many to swallow. General limits are frequently preferred.

(a) There was also an "enrichment factor" designed to account for nonuniform distribution of activity among particle sizes, but this was small and not considered very useful.

(b) Further action occurred in agency comments and supplementary information in an EPA Technical Report (520/4-78-010) whose availability was contained in a *Federal Register* notice in 1979 (FR 1979) and related documents (EPA 1978a,c). After a considerable period, "underground" guidance on transuranium elements in the general environment appeared in draft form as a *Federal Register* notice dated November 4, 1985 (EPA 1985). Three levels are proposed beginning at 1 mrad (10 μ Gy) per year to the pulmonary lung or 3 mrad (30 μ Gy) per year to the bone to a high, requiring monitoring and remedial action at doses not to exceed 500 mrem per year on an *intermittent basis*. Even this is still a draft so it appears that the pot still boils.

(c) This does not imply that all of the statements from other quarters relating to standards are as complete with derivations as would be needed to follow each item step-by-step.

3. The lack of gathering a true national consensus before important new regulations were proposed publicly was a cause of friction. Fortunately this has improved recently.
4. The need for new standards is doubted by many; it is insisted upon by many others.

The active participation of EPA considerably reduced the overt input to these subjects by the various laboratories in the internal emitter establishment, at least in the form of direct reports. They continued to participate, however, by individual or group participation, in the laborious hearing and commentary process. As we have seen; these have generated, for each proposed standard, volumes of arguments, statements of views, and much information on social and economic impact, etc., which played little part in the earlier standard-setting processes (chapter 16). A full description of these processes would require another book.

From the standpoint of this book, it is the difficulty of following the reasoning, not to mention the scientific basis in detail, that causes the most concern for many of the current and proposed standards for radionuclides in the environment. Since most of the levels producing problems are very low, there seems little doubt that the public health is being adequately protected. The dilemma is whether or not the cost is too high and unfair burdens are being placed upon one segment of the national enterprise. Since this is not a biomedical problem, no further comment is appropriate here.

We can conclude with a quotation from a paper given rather early in the development of these standards by Joyce P. Davis (Davis 1975). Dr. Davis combines a doctor of law degree with a bachelor's degree in physics and a master's degree in radiation biology, and has contributed some very informative and extremely well-balanced analyses of both the technical and legal problems of recent standard-setting activities. Her paper addressed the effect of the Federal Water Pollution Control Act (FWPCA) on NRC licensing jurisdiction and procedures. It included a capsule history that touched upon the National Environmental Policy Act of 1969 (NEPA) and the National Pollution Discharge Elimination System (NPDES). Her conclusions, including the prospects for a workable implementation of FWPCA are reproduced below:

The problems of cleaning up our nation's polluted waterways and of ensuring that all water bodies maintain a quality that permits their healthful use by man and other species on this earth are gigantic. Considerations of economics, ecology, and resource conservation must be carefully weighed in determining how resources of all types should be allocated to result in optimal benefit to the community.

The NPDES system establishes a framework for future action. One industry representative has referred to this framework as a skeleton needing to be clothed with muscle and flesh. Theoretically it creates a method whereby each source can contribute an equitable part to the maintenance of water quality, each source operator can know exactly what is expected of his facility, and enforcement can be facilitated. Whether this system will actually result in benefits to the natural and social environment depends not so much on the procedural aspects of the Act as on the substance of the effluent limitations actually set in the NPDES permits. The interpretation of the entire FWPCA will be reflected in the application of the permit system.

The effectiveness of the FWPCA could be substantially undermined by its overly rigid schedule of time deadlines; a lack of communication between industry and government and between government agencies; the possibility of duplication of efforts on, or even contention between, the EPA and other federal agencies or the federal and state levels of administration; the need for action in setting limitations

before adequate technical data are available; a lack of regard for the factors requiring individual rather than universally applicable limits; and a tendency to require "treatment for the sake of [t]reatment" or review for the sake of review. Any of these problems could become serious enough to severely hamper the efficacy of the permit program.

The EPA has recognized some of these difficulties and admits it is having "serious problems" implementing the FWPCA. The rigid time schedules are difficult to meet, and any slippage generally results in citizen suits to enforce them. The setting of "intelligent standards" for toxic pollutants within the time frame of the Act has been "virtually impossible," and the workload implications of the new requirements were not adequately anticipated. Some of the early regulations issued under the Act lack flexibility and may require modifications to make them workable. An EPA review and other studies have indicated that revision of the FWPCA effecting a relaxation of some of the deadlines and a change in the pace of spending for pollution control may be needed.

The opportunities presented by the new law are, however, correspondingly great. The NPDES provides a vehicle for defining, for every source, realistic, achievable, enforceable, and, above all, environmentally beneficial limits on effluent release. However, for these opportunities to be realized, all federal agencies, all levels of government, industry, and the scientific and technical communities must work together. There must be a free exchange of information and a willingness to evaluate in a single proceeding all aspects of the environment—natural, economic, and social—that are involved. If this can be done, the prospects for the FWPCA are excellent.

(Davis 1975)

V. Summary and Commentary

Some very sophisticated mixtures of engineering, aerosol physics, tracer chemistry, and biomedical science developed over the years to characterize the movement of radionuclides in the environment. Actually, it did not start with radioactivity problems. Industrial hygiene was well-developed in the pre-World-War-II years around the problems of air dispersion, air sampling, and aerosol characterization for nonradioactive dusts, fumes, and gases. But the large push in the atomic energy field contributed a leadership role. In recent years, modeling has occupied center stage. The field of environmental transport became, and is now, largely dependent on complex computer operations. In the eyes of some, the models have become living entities, transcending in importance the information they are supposed to correlate.

The first area to develop concerned airborne contamination. The industrial hygienists had provided a good start. In the early years, this area of our subject matter was almost a subsidiary of the field of industrial hygiene, including aerosol physics and meteorology. The primary focus was on the inhalation of any material, radioactive or nonradioactive, and its potential movement over geographically small areas. The general models developed in the 1930s for atmospheric diffusion; the role of turbulence, of particle size and composition, wind velocity and the like were applied in the 1940s et seq. to releases of radioactivity. Special attention was focused on equations developed to account for stack height and the presence or absence of obstructions such as buildings.

All of this later tied in with the larger-scale patterns of air movement found from the behavior of local and global fallout from nuclear weapons tests.

During the years of World War II, needs to know the movement of radionuclides in media other than air gradually developed. Terrestrial transport demanded considerable attention. In contrast to atmospheric transport, a major role of biota, especially vegetation, was found in the case of terrestrial transport. Naturally, the chemistry of the involved soil was a major consideration. Many of the more important variables turned out to be in the properties of soil and in soil-plant interactions.

Transport in surface water was, of course, an obvious need, particularly for systems such as the Columbia River, Clinch River, and, later, the Savannah River. Transport phenomena in rivers were found to be quite different from lakes, and estuaries different from the ocean. Biological systems were found to play important roles in surface water transport too. Biota move appreciable quantities of radionuclides in surface water systems. Models for freshwater food webs, compartments of a lake ecological system, and transformations within a body of water are shown.

The practice of disposing of radioactive wastes in pits and trenches focused attention, like the similar practice of dumping chemical wastes, on transport by ground water. Because of the exquisite sensitivity of radiation measuring instruments, minute leakages into ground water could be measured. Of special interest for radiation hazard evaluation is the very slow movement of ground water, except where fissures or cracks produce an underground stream. Biota play only a minor role in the transport of radionuclides in underground water.

An important endpoint of all of the environmental transport modeling was dietary pathways and usage. This entailed detailed research on dietary usage factors of numerous foodstuffs by infant, child, teen, and adult. To simplify the analysis of pathways, the International Commission on Radiological Protection suggested determining a "critical pathway" for each of various important circumstances. This was defined, of course, as the pathway that brought the most radionuclides to the ultimate recipient, humans. Along with this, the idea of a "critical population" was developed, this being that segment of the population, sometimes very small, that was predicted to have the largest intake from the critical pathway. These were, of course, nuclide-specific and system-specific. The idea provided a very useful simplification that was much needed in the days before rapid and comprehensive computer analyses, which can handle numerous pathways and populations almost simultaneously. In the case of mixtures, a third simplification, the "critical nuclide," was added. Examples are given of typical analyses based on these postulates.

As part of the growing volume of research information and the realization of the presence of concentration factors, as well as discrimination factors, it became obvious that radionuclides were recycled in the environment to a considerable extent. There were few "once-through" systems. The transport models had to take account of recycling,^(a) and anyone generating standards needed to be cognizant of these phenomena.

While recycling received much emphasis in aquatic and terrestrial systems, it also took a part in air transport. Hence, the fact that surface winds could

(a) Sometimes referred to as "reconcentration."

transport already deposited radioactivity to new sites by the process of "resuspension" was appreciated and utilized in models, particularly for arid environments. A single factor for resuspension was used in many analyses, even though the resuspension factor has a very large range.

Although many laboratories were involved in modeling the transport of radionuclides in the environment, the Hanford, Lawrence Livermore, and Oak Ridge groups have been especially involved. The chapter provides a summary of some of these efforts, plus the fact that much modeling has been done for preparation of environmental impact statements for nuclear facilities.

Isotopes of strontium, cesium, iodine, and of plutonium and the transplutronics have received sufficient attention with regard to their environmental transport to warrant specific summaries in this chapter. The work with strontium indicated that it was much less strongly complexed with the components of soil than many other important radionuclides. As a result, it remains quite mobile.

The work with cesium, among other things, brought out vividly how the characteristics of the ecosystem could influence environmental transfer. In the Arctic, a very short food chain exists: source-lichen-reindeer or caribou-human. As a result, cesium concentrations, arising from fallout, in residents of the far North were considerably higher than those in lower latitudes. Also, it was apparent that discrimination against cesium in the environment versus its homologue, potassium, was much less well developed than that for strontium over calcium.

Iodine transfer was, of course, of key importance in fallout from weapons tests. It is also among the more important potential effluents from nuclear installations. It was iodine transfer from the environment that first focused attention on the key role of food chains. Besides the experience with iodine in fallout, described in chapter 12, there were specific field tests. Among these were the Controlled Environmental Radioactive Tests that took place at Idaho Falls. These led to derivation of mathematical models for transfer to milk and prediction of the dose to humans. They, along with data from other sources, led to a drastic reduction in the allowable limit for iodine discharges from light-water-cooled reactors.

Plutonium and the transplutronics move relatively slowly in the environment, except when airborne. Because of their long half-life and damaging alpha-particle emission, these elements have received attention perhaps beyond their current biomedical significance as environmental hazards.

The chapter closes with a discussion of dose assessment for populations from environmental sources and for portions of the environment. This includes a fairly detailed review of ideas and methods for assessing radiation dose to populations and illustrations of the calculations made. Also, the development and use of the resuspension factors are reviewed because of the important part they have played in predicting population dose. Finally, environmental and population standards for drinking water, surface contamination, soil contamination, the effluents from light-water-cooled reactors, the uranium fuel cycle, and transuranics are reviewed briefly. Environmental transfer factors play an important role in the generation of all of these standards.

Important and sophisticated treatises are now available on the movement of radionuclides in the environment. Obviously, there are many gaps where "default" numbers must be used instead of actual data for the specific situation. However, the effort, begun in the years of World War II as described in chapter 11, has come far and can stand as a model for more general analyses of environmental contamination.

Note 1

Contents of book edited by Darryl Randerson entitled *Atmospheric Sciences and Power Production*, NTIS, Springfield, Virginia, 1984

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Note 2

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Hanford

- W. C. Hanson, H. E. Palmer, and B. I. Griffin. Radioactivity in Northern Alaskan Eskimos and their foods, Summer 1962. Chapter in *Project Chariot Environmental Program*.
- H. E. Palmer, W. C. Hanson, B. I. Griffin, and W. C. Roesch. 1962. *Radioactivity in Alaskan Eskimos*. Report HW-SA-2718, August 30, 1962. Also published in *Science* 142:64-65, with the title, Cesium-137 in Alaskan Eskimos, 1963.
- H. E. Palmer, W. C. Hanson, B. I. Griffin, D. M. Fleming. 1964. Radioactivity measurements in Alaskan Eskimos in 1963. *Science* 144:859-860.
- W. C. Hanson. 1966. Cesium-137 body burdens in Alaskan Eskimos during the Summer of 1965. *Science* 153:525-526.
- W. C. Hanson. *Cesium-137: Seasonal patterns in native residents of three contrasting Alaskan villages*. Report BNWL-SA-3002.
- W. C. Hanson. 1966. Fallout radionuclides in Alaskan food chains. *Amer. J. Vet Res.* 27:359.
- H. E. Palmer. 1965. Cesium-137 in Alaskans. *Science* 148:1115.
- H. E. Palmer, W. C. Hanson, B. I. Griffin, L. A. Braby. 1965. Radioactivity measured in Alaskan natives, 1962-1964. *Science* 147:620.
- W. C. Hanson, D. G. Watson, and R. W. Perkins. 1967. Concentration and retention of fallout radionuclides in Alaskan arctic ecosystems. In *Radiological concentration processes*. Symposium held in Stockholm, April 1966. Oxford-New York: Pergamon Press.

Lawrence Livermore Laboratory

- J. J. Koranda and J. R. Martin. 1971. Gamma-emitting radionuclides in Alaskan environments, 1967-1970. In *Proceedings of the 3rd National Symposium on Radioecology*, May 1971, U.S. AEC CONF-710501-P1, pp. 81-107. Oak Ridge, Tennessee.
- J. R. Martin and J. J. Koranda. 1971. Recent measurements of cesium-137 residence time in Alaskan vegetation. In *Proceedings of the 3rd National Symposium on Radioecology*, May 1971, U.S. AEC CONF-710501-P1, pp. 108-115. Oak Ridge, Tennessee.

Note 3

Contents of book edited by R. Scott Russell entitled, *Radioactivity and Human Diet*, 1966. Oxford-London-New York: Pergamon Press.

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- Aarkrog, A. 1971. Prediction models for strontium-90 and caesium-137 levels in the human food chain. *Health Phys.* 20:297-311.
- AEC. See Atomic Energy Commission.
- Anspaugh, L. R. and B. W. Church. 1983. Assessment of radiation doses downwind of the Nevada Test Site. In NCRP 1983, pp. 38-39.
- Anspaugh, L. R., J. H. Shinn, and D. W. Wilson. 1974. Evaluation of the resuspension pathway toward protective guidelines for soil contamination with radioactivity. In IAEA 1974, pp. 513-23.
- Anspaugh, L. R., P. L. Phelps, and N. C. Kennedy, and H. G. Booth. 1973. Wind-driven redistribution of surface-deposited radioactivity. In *Environmental behavior of radionuclides released in the nuclear industry*, pp. 167-84. Proceedings of a symposium held in Aix-en-Provence, May 14-18, 1973. Vienna: International Atomic Energy Agency.

- Anspaugh, L. R., J. H. Shinn, P. L. Phelps, and N. C. Kennedy. 1975. Resuspension and redistribution of plutonium in soils. *Health Phys.* 29:571-82.
- Atomic Energy Commission. 1973. *The potential radiological implications of nuclear facilities in the Upper Mississippi River Basin in the year 2000—The year-2000 study.* WASH-1209. Washington, D.C.: U.S. Atomic Energy Commission, Division of Reactor Development and Technology.
- Atomic Energy Commission. 1974a. *Environmental survey of the uranium fuel cycle.* WASH-1248. Washington, D.C.: U.S. Atomic Energy Commission.
- Atomic Energy Commission. 1974b. *Interim licensing policy on as low as practicable for gaseous radioiodine releases from light-water-cooled nuclear power reactors.* Regulatory guide 1.42, rev. 1. Washington, D.C.
- Auerbach, S. I. 1965. Radionuclide cycling: Current status and future needs. *Health Phys.* 11:1355-61.
- Bair, W. J. 1974. Considerations in assessing the potential harm to populations exposed to low levels of plutonium in air. In *Population dose evaluations and standards for man and his environment*, pp. 435-49. Proceedings of a symposium held at Portorož, Yugoslavia, May 20-24, 1974. Vienna: International Atomic Energy Agency.
- Baker, D. A., G. R. Hoenes, and J. K. Soldat. 1976. Food-air interactive code to calculate radiation doses from contaminated food products. In *Environmental modeling and simulation.* Proceedings of a conference held in Cincinnati, Ohio, April 19-22, 1976. Washington, D.C.: U.S. Environmental Protection Agency.
- Baker, T. P., B. B. Boecker, and J. L. Dick. 1958. Aircraft accidents involving plutonium contamination (U). AF5WC-TN-58-3. Kirtland Air Force Base, N. Mex.: U.S. Air Force Special Weapons Center.
- Barr, N. F. 1974. Assessment of potential health consequences of transuranium elements. In IAEA 1974, pp. 451-62.
- Bayer, A. 1972. Die Altersabhängigen Ingestions—Dosisfaktoren 8_G und $8_G'$ von Jod-131. *Keinforschungszentrum Karlsruhe*, KFK-1582.
- Beach, S. A. 1975. The identification of an homogeneous critical group using statistical extreme value theory: Application to laverbread consumers and the Windscale liquid effluent discharges. *Health Phys.* 29:171-79.
- Beninson, D. 1974. Population doses resulting from radionuclides of worldwide distribution. In IAEA 1974, pp. 227-33.
- Bernard, S. R. 1981. An urn model approach to actinide metabolism. In Wrenn 1981a, pp. 607-16.
- Bird, P. M., et al. 1965. *Cesium-137 in Northern Canada.* RPD-39. Ottawa, Canada: Department of National Health and Welfare, Radiation Protection Division.
- Blanchard, R. L. 1978. Criteria for the estimation of radiation dose. Personal communication from the Agency. Montgomery, Ala.: U.S. Environmental Protection Agency, Eastern Environmental Radiation Facility.
- Boecker, B. B. 1972. Personal communication from Department of Radiobiology, The Lovelace Foundation, Albuquerque, N. Mex., dated October 23, 1972.
- Booth, R. S. and S. V. Kaye. 1971. *A preliminary systems analysis model of radioactivity: Transfer to man from deposition in a terrestrial environment.* TM-3135. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Brenk, H. D., J. E. Fairbent, and E. H. Markee, Jr. 1983. Transport of radionuclides in the atmosphere. Chapter 2 in Till and Meyer 1983, pp. 2-1-2-86.
- Brodsky, A. 1980. Resuspension factors and probabilities of intake of material in process (Or "Is 10^{-6} a magic number in health physics?"). *Health Phys.* 39:992-1000.
- Bryant, P. M. 1964. Derivation of working limits for continuous release rates of iodine-131 to atmosphere in milk producing area. *Health Phys.* 10:249-57.
- Bunch, D. F., ed. 1966. *Controlled environmental radioiodine tests. Progress report number two.* IDO-12053. Springfield, Va.: National Technical Information Service.
- Bunch, D. F., ed. 1968. *Controlled environmental radioiodine tests. Progress report number three.* IDO-12063. Springfield, Va.: National Technical Information Service.
- Burnett, T. J. 1970. A derivation of the 'factor of 700' for ^{131}I . *Health Phys.* 18:73-75.

- Burton, C. A. and M. W. Pratt. 1968. *Prediction of the maximum dosage to man from the fallout of nuclear devices. III. Biological guidelines for device design*. UCRL-50163, pt. III (revised). Livermore, Calif.: Lawrence Radiation Laboratory.
- CAL. See California State Water Pollution Control Board.
- California State Water Pollution Control Board. 1952. *Water quality criteria*. Sacramento, Calif.
- Cataldo, D. A. and B. E. Vaughan. 1980. Interaction of airborne plutonium with plant foliage. In Hanson 1980, pp. 288-99.
- Cataldo, D. A. and R. E. Wildung. 1978. Soil and plant factors influencing the accumulation of heavy metals by plants. *J. Environ. Health Perspect.* 27:149-59.
- CEA/NRPB. See Commissariat à l'Energie Atomique/National Radiological Protection Board.
- Chamberlain, A. C. 1960. Aspects of the deposition of radioactive and other gases and particles. *Int. J. Air Pollution* 3:63-88.
- Chepil, W. S. 1945. Dynamics of wind erosion: II. Initiation of soil movement. *Soil Sci.* 60:397-411. [Note: This is one of a long series of papers by Chepil on wind erosion. See Healy 1980 for references.]
- Codell, R. B. and J. D. Duguid. 1983. Transport of radionuclides in groundwater. Chapter 4 in Till and Meyer 1983, pp. 4-1-4-53.
- Codell, R. B. and P. L. Schreiber. 1978. NRC models for evaluating the transport of radionuclides in groundwater. In *Management of low-level radioactive waste*, eds. M. W. Carter, A. A. Moghissi, and B. Kahn. New York-London-Oxford: Pergamon Press.
- Cohen, B. L. 1985. Transport of elements from soil to human diet: An alternative approach to pathway analysis. *Health Phys.* 49:239-45.
- Comar, C. L. 1953. Isotope methodology and miscellaneous agricultural applications. In Comar and Hood 1953, pp. 151-84.
- Comar, C. L. 1963. Factors influencing the biological availability of fallout radionuclides for animals and man. *Fed. Proc.* 22:1402-09.
- Comar, C. L. 1966. Transfer of strontium-90 into animal produce. In Russell 1966, pp. 249-75.
- Comar, C. L. and S. L. Hood, eds. 1953. *The role of atomic energy in agricultural research*, TID-5115. Proceedings of the 4th annual Oak Ridge summer symposium held in Oak Ridge, Tenn., August 25-30, 1952. Oak Ridge, Tenn.: Oak Ridge National Laboratory, Oak Ridge Institute of Nuclear Studies.
- Commissariat à l'Energie Atomique/National Radiological Protection Board. 1979. *Methodology for evaluating the radiological consequences of radiation effluents released in normal operations*. CEC report no. U/3865/79e.
- Cothorn, C. R. 1980. Letter to R. D. Evans, Scottsdale, Ariz., dated November 6, 1980.
- Cothorn, C. R. and W. L. Lappenbusch. 1985. Radioactivity in drinking water. *Health Phys.* 48(5):529-704. [Special issue.]
- Cuddihy, R. G. 1981. Modeling the metabolism of actinide elements. In Wrenn 1981a, pp. 617-28.
- Cummings, S. L., L. Bankert, A. R. Garrett, Jr., and J. E. Regnier. 1969. ¹³⁷Cs uptake by oat plants as related to the soil fixing capacity. *Health Phys.* 17:145-48.
- Dahlman, R. C. and P. Van Voris. 1976. Cycling of ¹³⁷Cs in soil and vegetation of a flood plain 30 years after initial contamination. In *Radioecology and energy resources*, ed. C. E. Cushing, Jr. Ecological Society of America special publ. no. 1, pp. 291-98. Proceedings of the 4th national symposium on radioecology held at Oreg. State Univ., May 12-14, 1975, Stroudsburg, Pa.: Dowden, Hutchinson & Ross, Inc.
- Daniels, R. S. 1983. Three Mile Island assessments. In NCRP 1983, pp. 83-93.
- DASA. See Defense Atomic Support Agency.
- Davis, J. P. 1975. The new federal water pollution control act and its impact on nuclear power plants. II: The effect of FWPCA on NRC licensing jurisdiction and procedures. *Nucl. Saf.* 16:421-33.

- Defense Atomic Support Agency. 1961. *The hazards and characteristics of plutonium and uranium contamination*. Albuquerque, N. Mex.: DASA, Nuclear Branch, Atomic Weapons Training Group, Field Command, Sandia Base.
- Defense Atomic Support Agency. 1972. Draft report on plutonium surface contamination levels for DoD action. [Classified "Official use only" and seen only in draft form.]
- Dick, J. L. 1972. Personal communication from him as general manager of EG&G, Inc., Albuquerque, N. Mex., December 1972.
- Dick, J. L. 1982. Personal communication from him as director of Division of Environmental Engineering and Research, Phelps Dodge Corp., Tucson, Ariz., July 10, 1982.
- Dick, J. L. and T. P. Baker. 1961. *Monitoring and decontamination techniques for plutonium fallout on large area surfaces*. Operation Plumbbob, Test Group 57, Program 73. WT-1512.
- Dunster, H. J. 1983. Windscale revisited—Condensed from the report of the National Radiological Protection Board, NRPB-R135, "An assessment of the radiological impact of the Windscale reactor fire, October 1957." In NCRP 1983, pp. 231-249.
- Durbin, P. W. 1974. *Transfer of plutonium from soil to plants: A review of the problem*. UCID-3689. Berkeley, Calif.: Lawrence Berkeley Laboratory.
- Durbin, P. W. 1986. Metabolic models for uranium. In *Biokinetics and analysis of uranium in man*, ed. R. H. Moore, USUR-05 HEHF-47, pp. F-1-F-65. Proceedings of a workshop sponsored by the U.S. Uranium Registry held in Richland, Wash., August 8-9, 1984. Richland, Wash.: Hanford Environmental Health Foundation.
- Durbin, P. W., J. Lynch, and S. Murray. 1970. Average milk and mineral intakes (calcium, phosphorus, sodium and potassium) of infants in the United States from 1954 to 1968; Implications for estimating annual intakes of radionuclides. *Health Phys.* 19:187-222.
- Durbin, P. W. and M. E. Wrenn. 1975. Metabolism and effects of uranium in animals. In *Conference on occupational health experience with uranium*, ERDA 93, pp. 67-129. Held in Arlington, Va., April 28-30, 1975. Washington, D.C.: U.S. Energy Research and Development Administration.
- Eisenbud, M. 1963. *Distribution of radioactivity in foods*. Fed. Proc. 22:1410-14.
- Eisenbud, M., P. Linsalata, and E. P. Franca. 1985. Use of natural analogues to predict the behavior of transuranic elements in the environment. In *Proceedings of the 21st annual meeting of the NCRP*, NCRP Proceedings no. 7, pp. 133-48. Held April 1985. Bethesda, Md.: National Council on Radiation Protection and Measurements.
- Eisenbud, M., K. Krauskopf, E. P. Franca, W. Lie, R. Ballad, P. Linsalata, and K. Fujiimori. 1984. Natural analogues for the transuranic actinide elements: An investigation in Minas Gerais, Brazil. *Environ. Geol. Water Sci.* 6:1-9.
- Ellis, M. M. 1937. Detection and measurement of stream pollution. *Bull. U.S. Bureau of Fisheries* 48:365-437.
- Energy Research and Development Administration. 1976. *Environmental research for transuranic elements*, ERDA-76/134. Proceedings of a workshop held in Seattle, Wash., November 1975. Springfield, Va.: National Technical Information Service.
- Environmental Protection Agency. 1972. *Environmental radioactivity surveillance guide*. ORP/SID 72-2. Washington, D.C.: U.S. Environmental Protection Agency, Office of Radiation Programs.
- Environmental Protection Agency. 1973. *Environmental analysis of the uranium fuel cycle. Part II. Nuclear reactors*. EPA-520/9-73-003.C. Washington, D.C.: U.S. Environmental Protection Agency, Office of Radiation Programs.
- Environmental Protection Agency. 1974. *Environmental radiation dose commitment: An application to the nuclear power industry*. EPA-520/4-73-002. Washington, D.C.: U.S. Environmental Protection Agency, Office of Radiation Programs.
- Environmental Protection Agency. 1975a. *Environmental radiation protection requirements for normal operations of actinides in the uranium fuel cycle*. Draft environmental statement. Washington, D.C.: U.S. Environmental Protection Agency, Office of Radiation Programs. Also *Federal Register*, 40(104):23420-25 (May 29, 1975).

- Environmental Protection Agency. 1975b. Interim primary drinking water regulations: Proposed maximum contamination levels for radioactivity. *Federal Register*, 40(158) (August 14, 1975).
- Environmental Protection Agency. 1976a. *Drinking water regulations—radionuclides*, Title 40, pt. 141. Pt. II. Washington, D.C.: U.S. Environmental Protection Agency, Office of Radiation Programs. Also *Federal Register* 41(133):28402-9 (July 9, 1976).
- Environmental Protection Agency. 1976b. *Quality criteria for water* Washington, D.C.: U.S. Environmental Protection Agency, Office of Radiation Programs. [Seen as a pre-publication copy—no number assigned.]
- Environmental Protection Agency. 1977a. *Proposed guidance on dose limits for persons exposed to transuranic elements in the general environment*. EPA 520/4-77-016. Washington, D.C.: U.S. Environmental Protection Agency, Office of Radiation Programs. Also *Federal Register* 42(230):60956-59., November 30, 1977, pp. 60956-59.
- Environmental Protection Agency. 1977b. *Radiological quality of the environment in the United States, 1977*. EPA 520/1-77-009. Washington, D.C.: U.S. Environmental Protection Agency, Office of Radiation Programs.
- Environmental Protection Agency. 1978a. *Response to comments: Guidance on dose limits for persons exposed to transuranium elements in the general environment*. EPA 520/4-78-010. Washington, D.C.: U.S. Environmental Protection Agency, Office of Radiation Programs.
- Environmental Protection Agency. 1978b. *Selected topics: Transuranium elements in the general environment*. EPA/ORP Technical Note CSD-78-1. Washington, D.C.: U.S. Environmental Protection Agency, Office of Radiation Programs.
- Environmental Protection Agency. 1978c. *The ecological impact of land restoration and cleanup*. EPA 520/3-78-006. Washington, D.C.: U.S. Environmental Protection Agency, Office of Radiation Programs.
- Environmental Protection Agency. 1981a. Draft Suggested Action Guidance (SAG)—Uranium. Letter from W. L. Lappenbusch to selected addressees submitting for review the EPA proposed guidance for uranium in drinking water, July 15, 1981.
- Environmental Protection Agency. 1981b. *Suggested Action Guidance—Uranium*. Circulated by Health Effects Branch, Criteria and Standards Division, United States Environmental Protection Agency, July 15, 1981. (Proposed as new part of National Interim Primary Drinking Water Regulations, EPA-57019-76-003.)
- Environmental Protection Agency. 1985. TRU guidance. *Federal Register* Notice, November 4, 1985. Washington, D.C.: U.S. Environmental Protection Agency, Office of Radiation Programs.
- EPA. See Environmental Protection Agency.
- ERDA. See Energy Research and Development Administration.
- Evans, R. D. 1975. Comments on EPA 40 CFR 141, FR, August 14, 1975. Letter to P. J. Nickles, Coving, and Burling, Washington, D.C., October 4, 1975.
- Evans, R. D. 1976a. Comments for the EPA Hearings on March 8-10, 1976, concerning the EPA Proposed Environmental Radiation Standards 40 CFR 190.
- Evans, R. D. 1976b. Letter to New Mexico Quality Control Commission, Santa Fe, on Proposed New Mexico Ground Water Regulations, June 25, 1976.
- Evans, R. D. 1980. Letter to W. L. Lappenbusch, Office of Drinking Water, EPA, September 8, 1980.
- Evans, R. D. 1981. Letter to W. L. Lappenbusch, Chief, Health Effects Branch, Office of Drinking Water, EPA, September 12, 1981, commenting on the EPASAG for uranium in drinking water.
- Federal Radiation Council. 1964. *Background material for the development of radiation protection standards*. Staff report no. 5, July 1964, Washington, D.C.
- Federal Register*. 1979. *Federal Register* 44:61104-5 (October 23, 1979).
- Federal Register*. 1980a. Interim cleanup standards for inactive uranium processing sites. *Federal Register*, 45:27366-68 (April 22, 1980). Washington, D.C.: Environmental Protection Agency.

- Federal Register*. 1980b. Proposed cleanup standards for inactive uranium processing sites, invitation for comment. *Federal Register* 45:27370-75 (April 22, 1980). Washington, D.C.: Environmental Protection Agency.
- Federation Proceedings*. 1963. *Nutrition symposium: Fallout, food, and man*. Symposium sponsored by the Federation of American Societies for Experimental Biology held at Atlantic City, N.J., April 20, 1963. *Fed. Proc.* 22:1389-1468.
- Fisher, H. L. 1972. *Prediction of the dosage to man from the fallout of nuclear devices 6. Transport of nuclear debris by surface and groundwater*. UCRL-50163, pt. 6. Livermore, Calif.: Lawrence Livermore Laboratory.
- Fletcher, J. F. and W. L. Dotson. 1971a. *HERMES—A digital computer code for estimating regional radiological effects from the nuclear power industry*. HEDL-TME-71-168. Richland, Wash.: U.S. Atomic Energy Commission, Hanford Engineering Development Laboratory.
- Fletcher, J. F. and W. L. Dotson. 1971b. Radiation dose model. Chapter written by J. K. Soldat and R. D. Harr. In Fletcher and Dotson 1971a.
- Foster, R. F. 1973. Observed versus theorized capacity of the environment for radioactive contaminants. In *Environmental behavior of radionuclides released in the nuclear industry*, STI/PUB/345, pp. 593-601. Proceedings of a symposium held at Aix-en-Provence, May 14-18, 1973. Vienna: International Atomic Energy Agency.
- Francis, C. W. 1978. *Radiostrotrium movement in soils and uptake in plants*. TID-27564. Washington, D.C.: U.S. Department of Energy, Technical Information Center.
- FRC. See Federal Radiation Council.
- French, N. R. 1967. Comparison of radioisotope assimilation by granivorous and herbivorous mammals. In *Radioecological concentration processes*, eds. B. Åberg and F. P. Hungate, pp. 665-73. Proceedings of a symposium held in Stockholm, April 25-29, 1966. Oxford-London-New York: Pergamon Press.
- French, N. R. and K. H. Larson. 1963. Environmental pathways of radioactive iodine from nuclear tests in arid regions. In *Radioecology*, eds. V. Schultz and A. W. Klement, Jr., pp. 77-81. Proceedings of the 1st national symposium on radioecology held at Colo. State Univ., September 10-15, 1961. New York: Reinhold Publishing Company; Washington, D.C.: American Institute of Biological Sciences.
- Garner, R. J. 1967. A mathematical analysis of the transfer of fission products to cows' milk. *Health Phys.* 13:205-12.
- Garner, R. J. 1972. *Transfer of radioactive materials from the terrestrial environment to animals and man*. Cleveland, Ohio: CRC Press. [Now Boca Raton, Fla.]
- George, K. D. 1970. ^{131}I reconcentration factor. *Health Phys.* 19:699.
- Gifford, F. A., Jr. 1961. Use of routine meteorological observations for estimating atmospheric dispersion. *Nucl. Saf.* 2:47-51.
- Gifford, F. A. 1976. Turbulent diffusion-typing schemes: A review. *Nucl. Saf.* 17:68-86.
- Golden, J. C. and R. A. Pavlick. 1974. A review of effluents, general population doses, and occupational doses resulting from Commonwealth Edison's use of nuclear power. In Hart, Ritchie and Varnadore 1974, pp. 173-80.
- Gossick, L. V. 1975. Letter to Russell E. Train, Environmental Protection Agency, enclosing comments from the Division of Operations of ERDA on the Proposed 40 CFR.190 Standards.
- Hanson, W. C. 1963. Iodine in the environment. In *Radioecology*, eds. V. Schultz and A. W. Klement, Jr., pages 581-601. Proceedings of the 1st national symposium on radioecology held at Colo. State Univ., September 10-15, 1961. New York: Reinhold Publishing Company; Washington, D.C.: American Institute of Biological Sciences.
- Hanson, W. C. 1967. Cesium-137 in Alaskan lichens, caribou and Eskimos. *Health Phys.* 13:383-89.
- Hanson, W. C., ed. 1980. *Transuranic elements in the environment*. DOE/TIC-22800. Washington, D.C.: U.S. Department of Energy, Technical Information Center.

- Hanson, W. C., D. G. Watson, and R. W. Perkins. 1967. Concentration and retention of fallout radionuclides in Alaskan arctic ecosystems. In *Radioecological concentration processes*, eds. B. Åberg and F. P. Hungate, pp. 233-45. Proceedings of a symposium held in Stockholm, April 25-29, 1966. Oxford-London-New York: Pergamon Press.
- Harley, J. H. 1983. Environmental radioactivity—Natural. In NCRP 1983, pp. 12-16.
- Harris, P. S. et al. 1956. *Contamination hazards from accidental non-critical detonation of small atomic devices*. LA-2079. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Hart, J. C., R. H. Ritchie, and B. S. Varnadore, eds. 1974. *Population exposures*, CONF-741018. Proceedings of the 8th midyear topical symposium of the Health Physics Society held in Knoxville, Tenn., October 21-24, 1974. Springfield, Va.: National Technical Information Service.
- Hawley, C. A., Jr., ed. 1966. *Controlled environmental radioiodine tests at the National Reactor Testing Station 1965 progress report*. IDO-12047. Springfield, Va.: National Technical Information Service.
- Hawley, C. A., Jr., C. W. Sill, G. L. Voelz, and N. F. Islitzer. 1964. *Controlled environmental radioiodine tests at the National Reactor Testing Station*. IDO-12035. Springfield, Va.: National Technical Information Service.
- Healy, J. W. 1957. *Calculations on environmental consequences of reactor accidents—Interim report*. HW-54128. Richland, Wash.: Hanford Atomic Products Operation.
- Healy, J. W. 1971. *Surface contamination: Decision levels*. LA-4558-MS. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Healy, J. W. 1974. *A proposed interim standard for plutonium in soils*. LA-5483-MS. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Healy, J. W. 1976a. *An examination of the pathways from soil to man for plutonium*. Los Alamos draft report, August 1967. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Healy, J. W. 1976b. *A review of resuspension models*. LA-UR-76-2767. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory. [Also in White and Dunaway 1977, pp. 211-22.]
- Healy, J. W. 1977. *An examination of the pathways from soil to man for plutonium*. LA-6741-MS. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Healy, J. W. 1980. Review of resuspension models. In Hanson 1980, pp. 209-35.
- Healy, J. W. 1984. Letter to J. N. Stannard, November 20, 1984.
- Healy, J. W. and J. J. Fuquay. 1958. Wind pickup of radioactive particles from the ground. In *Proceedings of the 2d United Nations international conference on the peaceful uses of atomic energy*. Held in Geneva, September 1-13, 1958. Geneva: United Nations. [Also in *Progress in nuclear energy*, ser. 12, Health Physics, eds. W. G. Marley and K. Z. Morgan, pp. 427-36. New York-London: Pergamon Press.]
- Healy, J. W. and J. C. Rodgers. 1978. *A preliminary study of radiation-contaminated soils*. LA-7391. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Healy, J. W., J. C. Rodgers, and C. L. Wienke. 1979. *Interim soil limits for D&D projects*. LA-UR-79-1865, rev. 46. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Heinemann, K. and K. J. Vogt. 1980. Measurements of the deposition of iodine onto vegetation and of the biological half-life of iodine on vegetation. *Health Phys.* 39:463-74.
- Hilst, G. R. 1955. *Measurements of relative wind erosion of small particles from various prepared surfaces*. HW-39356. Washington, D.C.: U.S. Atomic Energy Commission.
- Hoffman, F. O. 1973. *Environmental variables involved with the estimation of the amount of ^{131}I in milk and the subsequent dose to the thyroid*. Institute für Reaktorsicherheit der TÜV ev: IRS-W-6.
- Hoffman, F. O. 1977. A reassessment of the deposition velocity in the prediction of the environmental transport of radioiodine from air to milk. *Health Phys.* 32:437-42.

- Hoffman, F. O. 1978. A review of measured values of the milk transfer coefficient (f_m) for iodine. *Health Phys.* 35:413-16.
- Hoffman, F. O. and R. H. Gardner. 1983. Evaluation of uncertainties in radiological assessment models. Chapter 11 in Till and Meyer, pp. 11-1-11-55.
- Hoffman, F. O. and C. W. Miller. 1983. Uncertainties in environmental radiological assessment models and their implications. In NCRP 1983, pp. 110-38.
- Holm, E. and B. R. R. Persson. 1981. Comparative studies of natural and artificial α -emitters (actinides) in the lichen-reindeer-man food chain. In Wrenn 1981a, pp. 525-37.
- Hosker, R. P., Jr. 1979. Empirical estimation of wake cavity size behind block-type structures. In *Proceedings of the 4th symposium on turbulence, diffusion and air pollution*, pp. 603-9. Boston, Mass.: American Meteorological Society.
- Hull, A. P. 1974. As low as practicable: A critical initial appraisal of population health risks from power plant effluents. In Hart, Ritchie, and Varnadore 1974, pp. 161-72.
- Hunt, G. J. and J. G. Shepherd. 1980. The identification of critical groups. In *Radiation protection: A systematic approach to safety*, vol. 3, pp. 149-52. Proceedings of the 5th congress of the International Radiation Protection Association held in Jerusalem, March 9-14, 1980. Oxford-New York: Pergamon Press.
- Hvinden, T. and A. Lillegraven. 1961. Caesium-137 and strontium-90 in precipitation, soil and animals in Norway. *Nature* 192:1144-46.
- IAEA. See International Atomic Energy Agency.
- ICRP. See International Commission on Radiological Protection.
- International Atomic Energy Agency. 1974. *Population dose evaluation and standards for man and his environment*. Proceedings of a symposium held at Portorož, Yugoslavia, May 20-24, 1974. Vienna: International Atomic Energy Agency.
- International Atomic Energy Agency. 1976. *Transuranium nuclides in the environment*. Proceedings of a symposium held in San Francisco, November 17-21, 1975. Vienna: International Atomic Energy Agency.
- International Commission on Radiological Protection. 1965. *Principles of environmental monitoring related to the handling of radioactive materials*. ICRP publ. 7. Oxford-London-New York: Pergamon Press.
- International Commission on Radiological Protection. 1966. *Recommendations of the ICRP* (adopted September 17, 1965). ICRP publ. 9. Oxford-New York: Pergamon Press.
- International Commission on Radiological Protection. 1972. *The metabolism of compounds of plutonium and other actinides*. ICRP publ. 19. Oxford-New York: Pergamon Press.
- International Commission on Radiological Protection. 1973. *Alkaline earth metabolism in adult man*. ICRP publ. 20. Oxford-New York: Pergamon Press.
- International Commission on Radiological Protection. 1977. *Recommendations of the ICRP*. ICRP publ. 26, *Annals of the ICRP*, vol. 1, no. 3. Oxford-New York: Pergamon Press.
- Isherwood, D. 1981. *Geoscience data base handbook for modeling a nuclear waste repository*. NUREG/CR-0912, vols. 1 and 2. Washington, D.C.: U.S. Nuclear Regulatory Commission.
- Jaakkola, T., M. Keinonen, M. Hakanen, and J. R. Miettinen. 1981. Investigations of the transfer of plutonium and americium from plants to reindeer and man in Finnish Lapland. In Wrenn 1981a, pp. 509-23.
- Jacobs, D. G. 1983. Man-made sources released to the environment. In NCRP 1983, pp. 27-37.
- Jones, J. A. 1984. *A review of the work of the atmospheric dispersion modeling working group*. U.K. Radiological Protection Bulletin, no. 58, May 1984, ISSN 0308-4272.
- Kahn, B. 1983. Nuclear fuel cycle dose assesment. In NCRP 1983, pp. 94-109.

- Karches, G. J., J. K. Wheeler, G. L. Helgeson, and B. Kahn. 1969. Cesium-137 body burdens and biological half-life in children at Tampa, Florida, and Lake Bluff, Illinois. *Health Phys.* 16:301-13.
- Kathren, R. L. 1968. Towards interim acceptable surface concentration levels for environmental PuO_2 . In *Radiological protection of the public in a nuclear mass disaster*, CONF-68007, pp. 460-70. Proceedings of a symposium held in Interlaken, Switzerland, May 26-June 1, 1968. [Also BNWL-SA-1510. Richland, Wash.: Battelle-Northwest Laboratories.]
- Kathren, R. L. 1984. *Radioactivity in the environment: Sources, distribution, and surveillance*. New York: Harwood Academic Publishers.
- Kauranen, P. and J. K. Miettinen. 1967. ^{210}Po and ^{210}Pb in environmental samples in Finland. In *Radioecological concentration processes*, eds. B. Åberg and F. P. Hungate, pp. 275-80. Proceedings of a symposium held in Stockholm, April 25-29, 1966. Oxford-London-New York: Pergamon Press.
- Kaye, S. V., R. S. Booth, P. S. Rohwer, and E. G. Struxness. 1971. Cumulative exposure index (CUEX) for assessing environmental releases of radioactivity. In *Radioecology applied to the protection of man and his environment*, EUR-4800, vols. 1 and 2, pp. 909-22. Proceedings of a symposium held in Rome, September 7-10, 1971. European Atomic Energy Community.
- Klement, A. W., C. R. Miller, R. P. Minx, and B. Schlein. 1972. *Estimations of ionizing radiation dose in the United States—1960-2000*. ORP/CSD 72-1. Washington, D.C.: U.S. Environmental Protection Agency.
- Knapp, H. A. 1961. *The effect of deposition rate and cumulative soil level on the concentration of strontium-90 in U.S. milk and food supplies*. TID-13945. Washington, D.C.: U.S. Atomic Energy Commission.
- Langham, W. H. 1969. *Biological considerations of nuclear incidents involving nuclear warheads*. UCRL-50639. Livermore, Calif.: Lawrence Radiation Laboratory, Univ. of Calif.
- Langham, W. H. and J. W. Healy. 1973. Maximum permissible body burdens and concentrations of plutonium: Biological basis and history of development. Chapter 12 in *Uranium, plutonium, transplutonic elements*, eds. J. C. Hodge, J. N. Stannard, and J. H. Hursh, pp. 569-92. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.
- Lappenbusch, W. L. and C. R. Cothorn. 1982. Uranium in U.S.A. drinking water. *Health Phys.* 43:90 (Abstract P/5).
- Lappenbusch, W. L. and C. R. Cothorn. 1985. Regulatory development of the interim and revised regulations for radioactivity in drinking water—past and present issues and problems. *Health Phys.* 48:535-51.
- Leahy, E. J. and A. L. Smith. 1958. *Contamination control procedures for special weapons accidents*. USNRDL-TR-283. Washington, D.C.: U.S. Naval Radiological Defense Laboratory.
- Lengemann, F. W. 1970. Consumption of radionuclides from milk by man after radionuclide contamination of pastures: A predictive model. Paper presented at the 2d symposium on radioactivity and radiation biology and their significance for veterinarian medicine. Held in Hanover, Germany. *Zentralbl. Veterinärmed.* 11:77-87.
- Leonard, B. P., Jr. 1958. Hazards associated with fission product release. In *Proceedings of the 2d United Nations international conference on the peaceful uses of atomic energy*, vol. 11, pp. 157-70. Held in Geneva, September 1-13, 1958. Geneva: United Nations. [Also in *Progress in nuclear energy, A/Conf. 15/P/428*.]
- Lidén, K. 1961. Cesium-137 burdens in Swedish Laplanders and reindeer. *Acta Radiol.* 56:237-40.
- Lidén, K. and M. Gustafsson. 1967. Relationships and seasonal variation of ^{137}Cs in lichen, reindeer and man in Northern Sweden 1961-1965. In *Radioecological concentration processes*, eds. B. Åberg and F. P. Hungate, pp. 193-208. Proceedings of a symposium held in Stockholm, April 25-29, 1966. Oxford-London-New York: Pergamon Press.

- Liverman, J. L. 1975. Letter to Russell E. Train, Environmental Protection Agency [enclosing staff comments from ERDA Division of Biological and Environmental Research on Proposed EPA Regulations 40 CFR pt. 190. September 20, 1975].
- Liverman, J. L. 1976. Statement on proposed EPA rule-making on environmental radiation at hearing on standards for the uranium fuel cycle, March 8-10, 1976.
- Lloyd, R. D., R. C. Pendleton, D. O. Clark, C. W. Mays, and G. B. Goates. 1973. Cesium-137 in humans: A relationship to milk ^{137}Cs content. *Health Phys.* 24:23-36.
- Lucas, H. F. 1982. ^{226}Ra and ^{228}Ra in drinking water. *Health Phys.* 43:90 (Abstract P/6).
- Mahaffey, J. A., C. L. Sanders, G. E. Dagle, and J. F. Park. 1981. A comparison of Pu metabolism and pulmonary tumors in dogs and rats exposed to $^{239}\text{PuO}_2$. In Wrenn 1981a, pp. 541-55.
- Martin, A. and H. ApSimon. 1974. Population exposure and the interpretation of its significance. In IAEA 1974, pp. 15-26.
- Mattson, R. J. 1976. Statement presented at EPA hearing on Proposed 40 CFR pt. 190. March 8, 1976.
- Matuszek, J. M. 1983. A health physics evaluation of options for high-level radioactive waste disposal in the United States. In NCRP 1983, pp. 152-69.
- McDowell-Boyer, L. M. and C. F. Baes, III. 1980. Terrestrial food chain transport. In *Recommendations concerning models and parameters best suited to breeder reactor environment radiological assessments*, ORNL-5529. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- McKee, J. E. and H. W. Wolf. 1963. *Water quality criteria*. Publ. 3-A. Sacramento, Calif.: State Water Quality Control Board.
- McLendon, H. R., O. M. Stewart, A. L. Boni, J. C. Corey, K. W. McLeod, and J. E. Pinder. 1976. Relationships among plutonium contents of soil, vegetation and animals collected on and adjacent to an integrated nuclear complex in the humid southeastern United States of America. In IAEA 1976, pp. 347-61.
- Menzel, R. G. 1963. Factors influencing the biological availability of radionuclides for plants. *Fed. Proc.* 22:1398-1401.
- Miettinen, J. K. 1969a. Enrichment of radioactivity by arctic ecosystems in Finnish Lapland. In *Symposium on radioecology*, eds. D. J. Nelson and F. C. Evans, CONF-670503, pp. 23-31. Proceedings of the 2d national symposium on radioecology held in Ann Arbor, Mich., May 15-17, 1967. Springfield, Va.: National Technical Information Service.
- Miettinen, J. K. 1969b. The present situation and recent developments in the accumulation of ^{137}Cs , ^{90}Sr and ^{55}Fe in arctic foodchains. In *Environmental contamination by radioactive materials*, STI/PUB/226, pp. 145-51. Proceedings of a symposium held in Vienna, March 24-28, 1969. Vienna: International Atomic Energy Agency.
- Miettinen, J. K. and E. Häsänen. 1967. ^{137}Cs in Finnish Lapps and other Finns in 1962-6. In *Radioecological concentration processes*, eds. B. Åberg and F. P. Hungate, pp. 221-31. Proceedings of a symposium held in Stockholm, April 25-29, 1966. Oxford-London-New York: Pergamon Press.
- Milham, R. C., J. F. Schubert, J. R. Watts, A. L. Boni, and J. E. Corey. 1976. Measured plutonium resuspension and resulting dose from agricultural operations on an old field at the Savannah River Plant in the southeastern United States of America. In IAEA 1976, pp. 409-21.
- Miller, C. W. 1984. *Models and parameters for environmental radiological assessments: A critical review*. DOE/TIC-11468 (DE81027154). Washington, D.C.: U.S. Department of Energy.
- Mishima, J. 1964. *A review of research on plutonium releases during overheating and fires*. HW-83668. Richland, Wash.: Hanford Atomic Products Operation.
- Mitchell, N. T. 1974. Transfer of radionuclides to man through environmental pathways. In IAEA 1974, pp. 485-99.

- Moore, R. E.; C. F. Baes, III, L. M. McDowell-Boyer, A. P. Watson, F. O. Hoffman, J. C. Pleasant, and C. W. Miller. 1979. *AIRDOS-EPA: A computerized methodology for estimating environmental concentrations and dose to man from airborne releases of radionuclides*, ORNL-5532. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Morgan, K. Z. and E. G. Struxness. 1971. Criteria for the control of radioactive effluents. In *Environmental aspects of nuclear power stations*, STI/PUB/261, pp. 211-35. Proceedings of a symposium held in New York, August 10-14, 1970. Vienna: International Atomic Energy Agency.
- NAS. See National Academy of Sciences.
- NAS-NRC. See National Academy of Sciences-National Research Council.
- National Academy of Sciences. 1973. *Radionuclides in foods*. Washington, D.C.: U.S. NAS, Committee on Food Protection, Food and Nutrition Board.
- National Academy of Sciences-National Research Council. 1972. *Water quality criteria 1972*. Washington, D.C.: U.S. NAS-NRC, National Academy of Engineering.
- National Academy of Sciences-National Research Council. 1977. *Drinking water and health*. Reproduction under EPA auspices and with a forward by EPA of the Recommendations of the NAS. *Federal Register*, 42(132):35764-79 (July 11, 1977).
- National Council on Radiation Protection and Measurements. 1977. *Cesium-137 from the environment to man: Metabolism and dose*. NCRP report no. 52. Bethesda, Maryland.
- National Council on Radiation Protection and Measurements. 1983. *Environmental radioactivity*, NCRP proceedings no. 5. Proceedings of the 19th annual meeting of the NCRP held April 6-7, 1983. Washington, D.C.
- National Council on Radiation Protection and Measurements. 1984. *Radiological assessment: Predicting the transport, bioaccumulation, and uptake by man of radionuclides released to the environment*, NCRP report no. 76. Bethesda, Md.
- National Oceanic and Atmospheric Administration. 1979. *Assimilative capacity of U.S. coastal waters for pollutants*, ed. E. D. Goldberg. Washington, D.C.
- NCRP. See National Council on Radiation Protection and Measurements.
- Nevstrueva, M. A., P. V. Ramzaev, A. A. Moiseev, M. S. Ibatullin, and L. A. Teplykh. 1967. The nature of ^{137}Cs and ^{90}Sr transport over the lichen-reindeer-man-food chain. In *Radioecological concentration processes*, eds. B. Åberg and F. P. Hungate, pp. 209-15. Proceedings of a symposium held in Stockholm, April 25-29, 1966. Oxford-London-New York: Pergamon Press.
- Ng, Y. C. and S. E. Thompson. 1966. *Prediction of the maximum dosage to man from the fallout of nuclear devices. II. Estimation of maximum dose from internal emitters*. UCRL-50163, pt. II. Livermore, Calif.: Lawrence Radiation Laboratory.
- Ng, Y. C., et al. 1968. *Prediction of the maximum dosage to man from the fallout of nuclear devices IV. Handbook for estimating the maximum internal dose from radionuclides released to the biosphere*. UCRL-50163, pt. IV. Livermore, Calif.: Lawrence Radiation Laboratory.
- NOAA. See National Oceanic and Atmospheric Administration.
- Noshkin, V. E. 1972. Ecological aspects of plutonium dissemination in aquatic environments. *Health Phys.* 22:537-49.
- NRC. See Nuclear Regulatory Commission.
- Nuclear Regulatory Commission. 1975. *Reactor safety study*. Appendix VI. Calculation of reactor accident consequences. WASH-1400 (NUREG 75/014). Washington, D.C.
- Nuclear Regulatory Commission. 1977. *Calculation of annual doses to man from routine releases of reactor effluents for the purpose of evaluating compliances with 10 CFR Part 50, Appendix I*. Regulatory guide 1.109, rev. 1. Washington, D.C.
- Palms, J. M., V. R. Veluri, and F. W. Boone. 1975. The environmental impact of ^{129}I released by a nuclear fuel-reprocessing plant. *Nucl. Saf.* 16:593-602.
- Parker, H. M. 1956. Radiation exposure from environmental hazards. In *Proceedings of the international conference on the peaceful uses of atomic energy*, vol. 13, pp. 305-10. Held in Geneva, August 8-20, 1955, New York: United Nations.

- Parker, H. M. 1976. Statement on proposed EPA rule-making on environmental radiation at hearings on standards for the uranium fuel cycle, March 8-9, 1976.
- Parker, H. M. and J. W. Healy. 1956. Environmental effects of a major reactor disaster. In *Proceedings of the international conference on the peaceful uses of atomic energy*, vol. 13, pp. 106-9. Held in Geneva, August 8-20, 1955, New York: United Nations.
- Parzyck, D. C., J. P. Witherspoon, and J. E. Till. 1976. Validation of environmental transport models in the CUEx methodology. In *Radioecology and energy resources*, ed. C. E. Cushing, Jr., Ecological Society of America special publ. no. 1, pp. 194-98. Proceedings of the 4th national symposium on radioecology held at Oreg. State Univ., May 12-14, 1975. Stroudsburg, Pa.: Dowden, Hutchinson & Ross, Inc.
- Pasquill, F. 1962. *Atmospheric diffusion*. London: D. Van Nostrand Co.
- Pasquill, F. 1974. *Atmospheric diffusion*, 2d ed. New York: Ellis Harwood Limited.
- Pelletier, C. A. and J. D. Zimbrick. 1970. Kinetics of environmental radioiodine transport through the milk-food chain. In *Environmental surveillance in the vicinity of nuclear facilities*, ed. W. C. Reinig, pp. 257-67. Proceedings of the midyear topical symposium of the Health Physics Society held in Augusta, Ga., January 25, 1968. Springfield, Ill.: Charles Thomas.
- Pendleton, R. C. and W. C. Hanson. 1958. Absorption of cesium-137 by components of an aquatic community. In *Proceedings of the 2d United Nations international conference on the peaceful uses of atomic energy*, vol. 18, pp. 419-22. Held in Geneva, September 1-13, 1958. Geneva: United Nations.
- Pendleton, R. C., C. W. Mays, R. D. Lloyd, and B. W. Church. 1965. A trophic level effect on ^{137}Cs concentration. *Health Phys.* 11:1503-10.
- Persson, B. 1967. ^{59}Fe from fallout in lichen, reindeer and Lapps. In *Radioecological concentration processes*, eds. B. Åberg and F. P. Hungate, p. 253-258. Proceedings of a symposium held at Stockholm, April 25-29, 1966. Oxford-London-New York: Pergamon Press.
- Peterson, H. T., Jr. 1983. Terrestrial and aquatic food chain pathways. Chapter 5 in Till and Meyer, pp. 5-1-5-156.
- Poston, J. W. 1983. Reference man: A system for internal dose calculations. Chapter 6 in Till and Meyer, pp. 6-1-6-31.
- Preston, A. and D. F. Jeffries. 1969. The ICRP critical group concept in relation to the Windscale sea discharges. *Health Phys.* 16:33-46.
- Preston, A., N. T. Mitchell, and D. F. Jeffries. 1974. Experience gained in applying the ICRP critical group concept to the assessment of public radiation exposure in control of liquid radioactive waste disposal. In IAEA 1974, pp. 131-46.
- Price, K. R. 1971. *A critical review of biological accumulation, discrimination, and uptake of radionuclides important to water management practices—1943-1971*. BNWL-B-148. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Price, K. R. 1972. *Uptake of ^{237}Np , ^{239}Pu , ^{241}Am , and ^{244}Cm from soil by tumbleweed and cheatgrass*. BNWL-1688. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Price, K. R. 1973. A review of transuranic elements in soils, plants and animals. *J. Environ. Qual.* 2:62-66.
- Randerson, D., ed. 1984. *Atmospheric science and power production*, DE-84005177 (DOE/TIC 17601). Springfield, Va.: National Technical Information Service.
- Read, M. S. 1963. Countermeasures against radionuclides in foods. *Fed. Proc.* 22:1418-23.
- Rice, T. R. 1965. The role of plants and animals in the cycling of radionuclides in the marine environment. *Health Phys.* 11:953-64.
- Robison, W. L. 1983. Radiological dose assessments of atolls in the Northern Marshall Islands. In NCRP 1983, pp. 40-82.
- Romney, E. M. and J. J. Davis. 1972. Ecological aspects of plutonium dissemination in terrestrial environments. *Health Phys.* 22:551-57.

- Romney, E. M. and A. Wallace. 1977. Plutonium contamination of vegetation in dusty field environments. In White and Dunaway 1977, pp. 287-302.
- Romney, E. M., W. A. Rhoads, A. Wallace, and R. A. Wood. 1971. Persistence of radionuclides in soil, plants, and small mammals in areas contaminated with radioactive fallout. In *Radionuclides in ecosystems*, ed. D. J. Nelson, CONF-710501-P1, pp. 170-76. Proceedings of the 3d national symposium on radioecology held in Oak Ridge, Tenn., May 10-12, 1971. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Roswell, R. L. and M. E. Wrenn. 1980. An improved model for uranium metabolism in man. In *Research in radiobiology. Annual report of work in progress in the Internal Irradiation Program*, COO-119-256, pp. 115-28. Salt Lake City: Univ. of Utah.
- Rundo, J. and R. E. Toohey. 1983. Radon in homes and other technologically enhanced radioactivity. In NCRP 1983, pp. 17-26.
- Rupp, E. M. 1980. Age dependent values of dietary intake for assessing human exposures to environmental pollutants. *Health Phys.* 39:151-63.
- Rupp, E. M., F. L. Miller, and C. F. Baes, III. 1980. Some results of recent surveys of fish and shellfish consumption by age and region of U.S. residents. *Health Phys.* 39:165-75.
- Russell, R. S. 1960. Radioisotopes and environmental circumstances: The passage of fission products through food chains. In *Radioisotopes in the biosphere*, eds. R. S. Caldecott and L. A. Snyder, pp. 269-92. Proceedings of a symposium held in Minneapolis, October 19-23, 1959. Minneapolis: Univ. of Minn., Center for Continuation Study.
- Russell, R. S., ed. 1966. *Radioactivity and human diet*, p. 552. Oxford-New York: Pergamon Press.
- Schreckhise, R. G. and J. F. Cline. 1980. Comparative uptake and distribution of plutonium, americium, curium, and neptunium in four plant species. In Hanson 1980, pp. 361-70.
- Schwab, C. R. 1958. *Radiological safety in special weapons accidents*. USNRDL-TR-273. Washington, D.C.: U.S. Naval Radiological Defense Laboratory.
- Sehmel, G. A. 1977. Plutonium and tracer particle resuspension: An overview of selected Battelle-Northwest experiments. In White and Dunaway 1977, pp. 181-210.
- Sehmel, G. A. 1980a. Particle resuspension: A review. *Environ. Int.* 4:107-27.
- Sehmel, G. A. 1980b. Transuranic and tracer simulant resuspension. In Hanson 1980, pp. 236-87.
- Sehmel, G. A. 1981. Airborne plutonium-240 isotopic composition near Hanford. In *Pacific Northwest Laboratory annual report for 1980 to the DOE Assistant Secretary for Environment, Part 3 Atmospheric Sciences*, PNL-3700, pt. 3, pp. 95-110. Richland, Wash.: Pacific Northwest Laboratory.
- Sehmel, G. A. 1983. A relationship between plutonium activity densities of airborne and surface soils. *Health Phys.* 45:1047-50.
- Sehmel, G. A. 1984. Transuranic resuspension. In *Environmental research for actinide elements*. PNL-SA-11792. Proceedings of a DOE symposium held November 1983. Richland, Wash.: Pacific Northwest Laboratory.
- Skrable, K. W., G. E. Chabot, and M. Johnson. 1981. Retention functions. In Wrenn 1981a, pp. 559-606.
- Slade, D. H., ed. 1968. *Meteorology and atomic energy 1968*, TID-24190. Springfield, Va.: National Technical Information Service.
- Soldat, J. K. 1963. The relationship between I^{131} concentrations in various environmental samples. *Health Phys.* 9:1167-71.
- Soldat, J. K. 1965. Environmental evaluation of an acute release of I^{131} to the atmosphere. *Health Phys.* 11:1009-15.
- Soldat, J. K. 1971. *Modeling of environmental pathways and radiation doses from nuclear facilities*. BNWL-SA-3939. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Soldat, J. K. 1976. Radiation doses from iodine-129 in the environment. *Health Phys.* 30:61-70.
- Soldat, J. K., N. M. Robinson, and D. A. Baker. 1974. *Models and computer codes for evaluating environmental radiation doses*, BNWL-1754. Richland, Wash.: Battelle, Pacific Northwest Laboratories.

- Stewart, K. 1964. The resuspension of particulate material from surfaces. In *Surface contamination*, ed. B. R. Fish, pp. 63-74. Proceedings of a symposium held in Gatlinburg, Tenn., June 1964. New York-London: Pergamon Press.
- Strauch, S. 1971. The year 2000—Nuclear power and man. In *Radionuclides in ecosystems*, ed. D. J. Nelson, CONF-710501-P1, pp. 53-62. Proceedings of the 3d national symposium on radioecology held in Oak Ridge, Tenn., May 10-12, 1971. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Streng, D. L., W. E. Kennedy, Jr., and J. P. Corley. 1982. *Environmental dose assessment methods for normal operations at DOE nuclear sites*, PNL-4410. Richland, Wash.: Pacific Northwest Laboratory.
- Struxness, E. G., A. J. Luessenhop, S. R. Bernard, and J. C. Gallimore. 1956. The distribution and excretion of hexavalent uranium in man. In *Proceedings of the international conference on the peaceful uses of atomic energy*, vol. 10, pp. 186-96. Held in Geneva, August 8-20, 1955. New York: United Nations.
- Sulit, R. A., E. J. Leahy, and A. L. Baietti. 1961. *Principles of radiation and contamination control*. NAVSHIPS 250-341-3, vol. 3, p. 147. U.S. Department of the Navy.
- Tamplin, A. R. 1967. *Prediction of the maximum dosage to man from the fallout of nuclear devices. I. Estimation of the maximum contamination of agricultural land*. UCRL-50163, pt. I. Livermore, Calif.: Lawrence Radiation Laboratory.
- Tamplin, A. R., H. L. Fisher, and W. H. Chapman. 1968. *Prediction of the maximum dosage to man from the fallout of nuclear devices. V. Estimation of the maximum dose from internal emitters in aquatic food supply*. UCRL-50163, pt. V. Livermore, Calif.: Lawrence Radiation Laboratory.
- Tamura, T. 1977. Plutonium association in soils. In White and Dunaway 1977, pp. 97-114.
- Taylor, L. S. 1976. Testimony before the Environmental Protection Agency, March 8, 1976.
- Taylor, L. S. 1984. *The Tri-Partite conferences on radiation protection. Canada, United Kingdom, United States (1949-1953)*. NVO-271 (DE 84016028). Las Vegas: U.S. Department of Energy.
- Thompson, R. C. 1982a. Neptunium—The neglected actinide: A review of the biological and environmental literature. *Radiat. Res.* 90:1-32.
- Thompson, R. C. 1982b. Neptunium—The neglected actinide: Corrections and extensions. *Radiat. Res.* 90:1-32.
- Turner, D. B. 1969. *Workbook of atmospheric dispersion estimates*. Publ. no. 995-AP-26. Washington, D.C.: U.S. Department of Health, Education and Welfare.
- United Nations Scientific Committee on the Effects of Atomic Radiation. 1962. *A report of the United Nations Scientific Committee on the Effects of Atomic Radiation*. United Nations General Assembly, Official Report, 17th sess., suppl. no. 16 (A/5216), pp. 287-88. New York: United Nations.
- United Nations Scientific Committee on the Effects of Atomic Radiation. 1972. *Ionization radiation: Levels and effects*, vol. 1, levels E.72.IX.17. New York: United Nations.
- United Nations Scientific Committee on the Effects of Atomic Radiation. 1980. *Environmental behavior and dosimetry of radionuclides. Strontium-90*. United Nations General Assembly, 29th sess., September 1980. A/AC.82/R.382, January 21, 1980. (Prepared in the Secretariat.)
- UNSCEAR. See United Nations Scientific Committee on the Effects of Atomic Radiation.
- Vanderploeg, H. A., R. S. Booth, and F. H. Clark. 1976. A specific activity and concentration model applied to cesium-137 movement in a eutrophic lake. In *Radioecology and energy resources*, ed. C. E. Cushing, Jr. Ecological Society of America special publ. no. 1, pp. 164-77. Proceedings of the 4th national symposium on radioecology held at Oreg. State Univ., May 12-14, 1975. Stroudsburg, Pa.: Dowden, Hutchinson & Ross, Inc.

- Vaughan, B. E., R. E. Wildung, and J. J. Fuquay. 1976. Transport of airborne effluents to man via the food chain. In *Controlling airborne effluents from fuel cycle plants*, CONF-760806. Proceedings of a topical meeting of the American Nuclear Society. Oak Ridge, Tenn.: U.S. Atomic Energy Commission, Technical Information Center.
- Vaughan, B. E., J. K. Soldat, R. G. Schreckhise, E. C. Watson, and D. H. McKenzie. 1981. Problems in evaluating radiation dose via terrestrial and aquatic pathways. *J. Environ. Health Perspect.* 42:144-61.
- Wallace, A., E. M. Romney, and R. A. Wood. 1971. Cycling of stable cesium in a desert ecosystem. In *Radionuclides in ecosystems*, ed. D. J. Nelson, CONF-710501-P1, pp. 183-86. Proceedings of the 3d national symposium on radioecology held in Oak Ridge, Tenn., May 10-12, 1971. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Walsh, P. J., G. G. Killough, and P. S. Rohwer. 1978. Composite hazard index for assessing limiting exposures to environmental pollutants: Formulation and derivation. *Environ. Sci. & Tech.* 12:799-802.
- Water Quality Criteria. 1968. A report of the National Technical Advisory Committee to the Secretary of the Interior, Washington, D.C.
- Watters, R. L. 1981. Ecological transport. In Wrenn 1981a, pp. 503-7.
- Watters, R. L., D. N. Edgington, T. E. Hakonson, W. C. Hanson, M. H. Smith, F. W. Whicker, and R. E. Wildung. 1980. Synthesis of research literature. In Hanson 1980, pp. 1-44.
- Whicker, F. W. and V. Schultz. 1982. *Radioecology: Nuclear energy and the environment*, vols. 1 and 2. Boca Raton, Fla.: CRC Press.
- White, M. G. and P. B. Dunaway, eds.. 1977. *Transuranics in natural environments*, NVO-178. Proceedings of a symposium held in Gatlinburg, Tenn., October 1976. Las Vegas: Nevada Applied Ecology Group, U.S. Energy Research and Development Administration.
- Wildung, R. E., T. R. Garland, and D. A. Cataldo. 1979. Environmental processes leading to the presence of organically bound plutonium in plant tissues consumed by animals. In *Biological implications of radionuclides released from nuclear industries*, STI/PUB/522, vol. 2, pp. 319-34. Proceedings of a symposium held in Vienna, March 26-30, 1979. Vienna: International Atomic Energy Agency.
- Wilson, D. J. 1979. Flow patterns over flat-roofed buildings and applications to exhaust stack design. *ASHRAE Transactions* 88:284-95.
- Wilson, D. W., G. M. Ward, and J. E. Johnson. 1969. A quantitative model of the transport of ^{137}Cs from fall-out to milk. In *Environmental contamination by radioactive materials*, STI/PUB/226, pp. 125-34. Proceedings of a symposium held in Vienna, March 24-28, 1969. Vienna: International Atomic Energy Agency.
- Wilson, R. H., R. G. Thomas, and J. N. Stannard. 1960. *Biomedical and aerosol studies associated with a field release of plutonium*. WT-1511. Springfield, Va.: National Technical Information Service.
- Witherspoon, J. P. 1974. Population exposure estimates as derived from an environmental assessment of LWR fuel cycle facilities. Part I. Population doses from operation facilities. In Hart, Ritchie, and Varnadore 1974, pp. 191-98.
- Witherspoon, J. P. and D. C. Parzyck. 1974. Population exposure estimates as derived from an environmental assessment of LWR fuel cycle facilities. Part II. Long-term population doses following cessation of plant operations. In Hart, Ritchie, and Varnadore 1974, pp. 199-206.
- Wrenn, M. E. 1981a. *Actinides in man and animals*. Proceedings of the Snowbird actinide workshop held in Snowbird, Utah, October 15-17, 1979. Salt Lake City: RD Press.
- Wrenn, M. E. 1981b. Discussion [after papers on uranium] in Wrenn 1981a.
- Wrenn, M. E. 1984. Personal communication enclosing planned EPA standards on uranium in drinking water and testimony before the Colorado Water Control Commission.
- Wrenn, M. E., T. Lo Sasso, and P. W. Durbin. 1977. A metabolic model for uranium metabolism in man. In *New York University Annual Report*, CDO-3382-16, pp. X1-1 to X1-16.

- Wrenn, M. E. and R. L. Roswell. 1980. *Derivation of exposure limits for uranium*. Draft report from Univ. of Utah, February 1980.
- Wrenn, M. E., P. W. Durbin, B. Howard, J. Lipsztein, J. Rundo, E. T. Still, and D. L. Willis. 1985. Metabolism of ingested U and Ra. *Health Phys.* 48:601-33.
- Zimbrick, J. D. and P. G. Voillequé, eds. 1969. *Controlled environmental radioiodine tests at the National Reactor Testing Station—Progress report number four*. IDO-12065. Springfield, Va.: National Technical Information Service.

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Capsule Chronology^(a)

- 1925 International Congress of Radiology organized.
- 1928 Organization and first meeting of International Committee on X-ray and Radium Protection (predecessor of ICRP).^(b)
 Organization of U.S. Advisory Committee on X-ray and Radium Protection (predecessor of NCRP). First meeting in 1929.
- 1941 Formulation of standards for radium and radon (NBS; Evans and Goodman). Based directly on data concerning effects in humans for radium, and atmosphere in mines for radon.
- 1942–1945 Several standards developed on more or less individual basis for the MED operations (see also earlier chapters).
- 1944 Air limits for plutonium derived at Met Lab.
 Exposure standard for natural uranium set arbitrarily by analogy to lead.
- 1945 Landmark paper by Cantril and Parker on tolerance dose.
 Morgan circulates first comprehensive calculations of maximum permissible body contents and concentrations in air and water for many radionuclides in a Met Lab Report called "Tolerance Concentrations."
- 1945–1946 Inhalation experiments at Rochester made basis for revision of standard for uranium. Different levels recommended for soluble versus insoluble salts.
- 1945 et seq. Standards developed for plutonium on basis of animal toxicity data. Earliest attempts are on basis of half-life relative to radium, but animal work proves this to be incorrect.
- 1946 Reorganization of U.S. Advisory Committee. Renamed National Committee on Radiation Protection and operates out of the Bureau of Standards. Has two subcommittees on radionuclide problems.
- 1947 Publication of Morgan's compendium on tolerance concentrations of radioactive substances. The computational approach.
 Parker describes standard setting and operational limits used in MED operations and important principles.
- 1949 First Tri-Partite Conference on Internal Dosimetry (Chalk River, Ontario). Accumulated experience of the war years utilized.
- 1950 Need for better relative toxicity data for bone seekers generates the Utah project and expansion of Argonne work.
 Second Tri-Partite Conference on Internal Dosimetry (Buckland House, Harwell, U.K.).
- 1950s AEC develops regulations for individual radionuclides under occupational exposure conditions.

(a) Many of the events pertinent to the subjects of this chapter have already been cited and will not be repeated here, unless of special importance.

(b) For abbreviations and acronyms, see Appendix D.

- 1951 First organizational recommendations since 1941 for permissible levels of radionuclides, primarily from NCRP.
- 1953 Third Tri-Partite Conference on Internal Dosimetry (Arden House, Harriman, New York).
- 1954 Indications appear that tissue burdens of uranium in man are lower than predicted by models (Eisenbud and Quigley, AEC).
- 1955 Formulation of standards for single exposures (Morgan, Snyder, Ford).
United Nations Scientific Committee (UNSCEAR) organized to gather information, much of it pertinent to standard setting.
- 1956 Indications that uranium may be less toxic to humans than animal experiments predicted (Eisenbud).
Early reports of strontium metabolism in man (Comar, Laszlo, Spencer).
- 1957 American Council of Governmental Industrial Hygienists suggests a single value for air concentration of both soluble and insoluble natural uranium.
- 1958 Bureau of Radiological Health organized within U.S. Public Health Service.
- 1959 Report of Committees 2 of NCRP and ICRP on occupational limits for exposure to radionuclides. Utilizes dual system; uses effects directly for radium and bases other bone seekers on it; uses the computational approach for all others using external radiation effects as basis.
Federal Radiation Council (FRC) formed to advise the U.S. President about radiation matters, especially standards. Series of reports issued. See below and chapters 3, 12, and 15.
- 1960 First series of BEAR reports issued by NAS-NRC. Does not address standards directly, but contains much pertinent information.
- 1960s Large effort at Oak Ridge on trace elements in human tissue (Tipton).
Beginning of population exposure standards (chapter 15).
AEC develops elaborate code of Federal Regulations for radionuclide exposure (10 CFR 20 et seq.). Patterned after 1959 ICRP/NCRP reports, but adds population exposure limits by use of a scaling factor.
- 1960-1961 First two reports from FRC on basic radiation protection guides. Introduces formally the concept of balancing risks and benefits.
- 1962 FRC Report No. 3 on health implications of fallout.
One of several Congressional hearings on fallout starts. Several bear on standards and their validity (see earlier chapter listings).
- 1963 FRC Report No. 4 on estimates and evaluation of fallout in the United States through 1962.
A second Congressional hearing including Radiation Standards and Fallout.
- 1964 FRC Report No. 5—more on development of standards.
FRC Report No. 6—revised standards for fallout.

- 1964** NCRP becomes a Congressional Charter Organization and is named National Council on Radiation Protection and Measurements.
- 1965** FRC Report No. 7—Protective Action Guides for ^{89}Sr , ^{90}Sr , ^{137}Cs .
- 1966** Publication of new lung model from ICRP Task Group on Lung Dynamics.
Publication of model for dosimetry of gastrointestinal tract by Eve and Dolphin and Eve, United Kingdom.
- 1968** ICRP Report on handling single intakes. Time integral of dose utilized.
U.S. Transuranium Registry organized. Data especially pertinent to validation of standards.
- Late 1960s** Congress institutes environmental impact statement as result of Calder Hall case. A new phase begins in population dose standards and protection.
- 1970** EPA takes over standard-setting functions for the environment. Later to be shared with Nuclear Regulatory Commission.
- 1970s** NAS-NRC BEIR committee begins work on evaluation of low-level radiation exposure.
National Environmental Protection Act changes status of all environmental protection standards.
- 1971** Large LLL report on elemental concentrations in human organs (Anspaugh et al.).
Review of data from the eighteen patients injected with plutonium (chapter 7) validates most of the original metabolic data (Durbin at Berkeley).
Lauriston Taylor's short book on history of standard setting published.
- 1972** The ICRP bone dosimetry model (Marshall model) is published.
First report of mortality experience in uranium workers (Scott et al. at Oak Ridge).
- 1973** Hursh and Spoor review data for uranium in man.
Remeasurements of plutonium patients (Rundo, ANL).
Complete review of twenty-five Los Alamos workers from MED days (Hempelmann, Richmond, Voelz).
Cancer statistics among uranium workers reviewed (Archer et al., Salt Lake City).
- Mid-1970s** AEC disbanded. Regulatory and standards-setting functions transferred to new Nuclear Regulatory Commission for application to licensees. Agencies still have some jurisdiction over own operations. EPA assumes jurisdiction over general environmental aspects.
- 1975** ICRP Report on Reference Man published. Result of years of effort in many laboratories. Used for nearly all dose calculations and assessments.
First reports on epidemiology of uranium indicate standards have been adequate but need more follow-up.
Hursh's review of origin and basis of standards for uranium.

- 1975 Code of Federal Regulations modified to account for role of food chain in transport of radionuclides. Appendix I of 10 CFR 50 mandates large reduction of limits for effluents from light-water-cooled reactors. (Prepared May 5, 1975, effective June 4, 1975.)
- 1977 Los Alamos resident survey.
- 1977-1979 Mancuso studies reported. Generates considerable polemic.
- 1978 ICRP Publication-30 approved on Limits for Intakes of Radionuclides by Workers. Discards direct approach for bone seekers and concentrates on computational approach for all radionuclides. Followed by several supplements that give details for hundreds of nuclides utilizing computerized retrieval and use of metabolic data accumulated over several decades. Published in 1979.

U.S. Uranium Registry established. Very important to future validation of standards.
- 1979 A further complete review of the Los Alamos MED workers (Voelz). Results appear to validate even the old high standards, but group too small for epidemiologic significance.

Lauriston Taylor's large book on history of ICRP and NCRP published.
- 1980 Reports on health of thorium factory workers do not validate the high toxicity assigned to radiothorium by the computational approach.
- 1981 Evans's review of development of radium standards.

Parker's review of wartime operations and standards, especially vis-à-vis plutonium.

Stannard reviews uses of laboratory research in setting standards for exposure to radionuclides.

Taylor reviews standards.

Information on americium case from Richland helps with validation process (U.S. Transuranium Registry).

Reports of late excretion rates of plutonium following acquisition of known amounts (Rundo, ANL).

Further data on mortality of Oak Ridge uranium workers (Polednak and Frome).
- 1982 Report of tissue contents of plutonium from 180 autopsy cases dying from natural causes (McInroy, Los Alamos).
- 1983 Formal report on over 19,000 Tennessee Eastman employees. Some potential excess risks found, but not proven yet (Cookfair et al.).

Chapter 16

Internal Emitter Research and Standard Setting: Validation In Man

Overview

In this chapter, we show how the research findings reviewed in this book have been and are being applied to the process of limiting intakes of radionuclides so that the amounts deposited and retained in the body are kept within acceptable limits. We also consider briefly some of the applications of the research to problems of environmental limits discussed in chapter 15.

The motivation for the early biomedical research work with radioactive materials was primarily (1) to establish the behavior and biological effects of deposited radionuclides and (2) to use the information to develop standards. There is no doubt that the enviable overall occupational health record of the atomic energy industry could not have been achieved without the products of these research efforts. Conversely, where the research and its application were neglected in the early days, the health record has not been so enviable (e.g., the uranium miners).

Before considering how the results were used, the chapter digresses for a short review of the organizations and some of the key individuals involved in the process. This is by no means a history of radiation protection philosophy or activities. There is enough detail, however, to aid in comprehension of the systems to which the research data were applied, including some of the basic formulations. Details are reserved for chapter 20.

We then examine in some depth those standards that can be said to have been derived directly from experience and experiment. This is termed "Direct Derivation of Standards." The elements discussed are radium, radon, uranium, plutonium, ^{224}Ra , and ^{232}Th . There is also a short discussion of the approach of the Federal Radiation Council, since it utilized primarily direct derivations.

Obviously, the number of elements with sufficient information for direct derivation of standards is relatively small. The others, including the hundreds of new radionuclides produced in nuclear fission, required an indirect approach. We have termed this "The Computational Approach." It involved the design of a general system that allowed computation of maximum permissible body burdens and maximum allowable concentrations in air and water by use of the

metabolic information on behavior of the substances of interest. The two-pronged approach, one for elements that localize in bone, the other for elements that do not localize in bone, is described. The special features of the computational system, along with later modifications for single and population exposures, are touched upon lightly, as is the important work on determining concentrations of stable elements.

The research information on radionuclides has contributed most heavily to the establishment of retention kinetics, general metabolic models, and special models such as those for lung and gastrointestinal tract. The latter two, along with the construction of Reference Man (Standard Man), required much use of basic physiological, biochemical, and anatomical knowledge as well, but the slant was always toward development of standards. This is reviewed in two sections on modeling.

The last major section of the chapter considers work bearing on the validation of the standards already developed, largely by work involving humans. This embraces the validation of both the metabolic models and the basic standards themselves by means of autopsy programs and a growing cadre of epidemiologic projects. Included are the patients and workers exposed to plutonium and the development of the U.S. Transuranium Registry; validation of models and limits for uranium, including the relatively new U.S. Uranium Registry, and the quite new epidemiologic work at Oak Ridge on former Manhattan Engineer District uranium workers; and the fission products, especially strontium and iodine. It is concluded that by and large the models and limits have been and are being satisfactorily validated with some exceptions, the most notable of which is uranium, where both the amounts deposited and toxic effects in human kidney are considerably below predictions. Another exception concerns the environmental behavior of certain nuclides such as iodine where the amounts permitted to enter the environment have had to be lowered very substantially. Plausible explanations are given for each major deviation from expected behavior.

In the final section, labeled "Epilogue," we see that scientific information *per se* is now having less effect on standard setting, both for radionuclides and for other potential hazards than it did in the primary period of this book. This is because the proposed levels are getting so low that it appears almost impossible to design scientific experiments that can prove or disprove a given hypothesis for a dose-effect relationship. The scientific data input to metabolic models and to environmental models continues of major importance, however. Finally, the chapter emphasizes that new efforts should be directed toward the estimation of risk from deposited radionuclides.

I. Introduction

This chapter represents to some degree a synthesis of much that we have reviewed to this point. The purposes of the various lines of research have been multiple. In addition to the usual scientific motivation to obtain new knowledge and to test hypotheses, anticipated applications to the setting and validation of occupational and population limits of exposure and intake of radionuclides have been of primary importance. Only applications to medicine, to the problems of handling radioactive materials, and the behavior of radionuclides in the environment have approached in importance the practical objective of standard

setting. Indeed, parts of the earlier programs, especially in the days of the Manhattan Engineer District (MED), were almost totally oriented toward obtaining information that could be utilized *almost immediately* for establishing maximum permissible intakes, body and organ burdens (Friedell 1983).

A corollary to the generation of new data that could be used in standard setting has been the need to examine in retrospect *in humans* the validity of the limits imposed. Since the limits are all at levels where overt biomedical effects are extremely unlikely, this validation process has applied more to checking out in man the many metabolic parameters applied than to incidence of effects, with a few exceptions. However, incidence of any and all possible biomedical effects has been diligently explored. In the case of ^{226}Ra , ^{224}Ra , and ^{222}Rn and its progeny, where the intakes preceded or ignored the developing standards, there has been a continuous opportunity to accomplish direct validation in man in terms of effects. For many other radionuclides, the search for effects has had to become retrospective epidemiology.

The chapter will perforce consider some of the organizations that utilized the research data and the manner in which they focused the results of research onto the standard-setting process. We will need to consider some of the divisions of responsibility developed over the years. However, we will in no sense attempt a formal history of the people and organizations engaged in radiation protection or its philosophy. These have already been expounded in depth by professionals who have devoted their lives to the process. Convenient among these for our purposes are Lauriston Taylor's reviews at the first Atoms for Peace Conference (Taylor 1956a,b), his short book (Taylor 1971), his historical review at the silver anniversary meeting of the Health Physics Society (Taylor 1981), and his monumental treatise drawing together nearly every documented activity of the International Commission on Radiological Protection (ICRP), the U.S. National Council on Radiation Protection and Measurements (NCRP) and their predecessors, and correlated activities in the radiological community (Taylor 1979).

Despite its size, the large Taylor compendium purposely leaves blank the section intended to deal with the 1941 to 1946 years of the atomic energy project in the United States, i.e., the MED. He states his hope that H. M. Parker, "who was involved in the radiation safety project^(a) from the outset, and who brought to the project many years of experience in the medical physics field, will someday fill in this most important gap" (Taylor 1979, p. 6-001). Fortunately, although it was necessarily somewhat abbreviated, Parker did give the essence of the development and operation of the Plutonium Project Protection Programs at the Health Physics Twenty-Fifth Anniversary Meeting (Parker 1981).^(b) This updated an MDDC report declassified in 1947 (Parker 1947 and 1980). The report is comprehensive and goes well beyond Manhattan Project experience. It involves instrumentation and procedures in depth as well as organizational aspects. It is exceeded in depth and usefulness only by what must now be regarded as a true classic of the era, the paper on the "tolerance dose" prepared

(a) At Clinton Laboratories and the Metallurgical Laboratory first, but primarily at Hanford.

(b) Taylor's original wish can never be completely fulfilled since Mr. Parker is no longer with us.

by Cantril^(a) and Parker in 1945 while the operations were still at the Clinton Laboratories at Oak Ridge (Cantril and Parker 1945).

Further details are contained in another summary from the 1940s prepared by Karl Z. Morgan and reproduced in the Health Physics Society's Twenty-Fifth Anniversary volume (Morgan 1946 and 1980).^(b)

A recent compendium of special usefulness because of the variety of subjects included is the result of a special conference called "Health Physics: A Backward Glance" (Kathren and Ziemer 1980), developed at a meeting of the Hoosier chapter of the Health Physics Society. The first paper in this volume gives a review of the first fifty years of radiation protection.

For a smorgasbord of essentially every aspect of radiation protection, the several hearings of the Congress of the United States held under the auspices of the Joint Committee on Atomic Energy are especially useful. One two-volume set with over two thousand pages is devoted to broad discussions of radiation protection criteria (U.S. Congress 1960a,b). The witnesses cover every conceivable segment of the field and most organizations or jurisdictions with a legitimate interest in the subject. These volumes are, of course, unedited and do not take up the polemics which arose in later years. Nevertheless, the hearings provide a comprehensive review of both historical developments and contemporary problems.^(c) With these reviews and the cited literature therein, a reasonably comprehensive overview can be gleaned.^(d) Our task now is to pinpoint how the research operations nurtured these activities as they apply to standards for radionuclides. However, we must first examine briefly the people and organizations involved.

II. Who's Who

Even though we are consciously eschewing any attempt at a comprehensive history of radiation protection, it is important to identify the organizations and some of the principal people we will be relating to in this chapter. Those organizations that are known well and whose origins and history are readily available will be considered relatively briefly. Some others whose characteristics and

(a) Sidney Cantril was a close colleague of H. M. Parker beginning during their days at Swedish Hospital in Seattle.

(b) Obviously, the reports just cited do not pertain organizationally to other than the MED and its contractors since this was the milieu in which the developments took place. The Taylor syntheses on the other hand concern largely ICRP, NCRP, the National Bureau of Standards, and organized radiology and radiological physics.

(c) There were, in addition, hearings on specific problems such as the uranium miners (see later sections of this chapter).

(d) Whole sessions at numerous symposia and congresses have been devoted to overviews of radiation protection practices around the world. They can be found easily in the cited literature in this book. Also, anyone interested in a strictly chronological review will find the volume prepared by Robert I. Bell at Auburn University extremely useful (Bell 1977). This is encyclopedic with short notes on events from 1661 to 1977. Obviously, the first part is early physics and chemistry, that gradually flows into radiobiology and then into development of protection standards. Having struggled to find when certain events took place, certain procedures evolved, certain organizations were founded, etc., this author can readily appreciate the magnitude of the task, which Bell, with help from his family and his university, undertook. Since the volume is privately printed, the author's full address is given in the bibliography.

contributions need special attention to assure their recognition by posterity are taken up in greater detail.

We will arbitrarily divide the groups into those whose primary function has been the formulation of *recommendations* and those whose function was (and is) the establishment of *regulations* with the force of law. Sometimes the recommendations were translated almost verbatim into regulations, but that was the choice of the regulators and in no way negates the basic difference in intent.

A. The Advisors

1. Early Organizations

The International Committee on X-ray and Radium Protection. The radiological societies of a number of countries organized an International Congress of Radiology in 1925 (Taylor 1979). They realized that radiation protection would assume greater importance as radiology grew. Several member societies prepared proposals for some sort of international committee on radiation protection. This came to fruition in 1928 with the organization and first meeting of what was called the International Committee on X-ray and Radium Protection. This was part of the Second International Congress of Radiology held in 1928. The organization continued as an affiliate of the International Congress organization.

Official recommendations were issued about every three years except for the period 1938 to 1949. Most of these concerned external radiation sources. Except for a small secretariat, all those serving on the committee were volunteers.

The U.S. Advisory Committee on X-ray and Radium Protection. As described by Taylor (1979), a need appeared for individual countries to “present a more consolidated position with regard to national needs” and in preparation for international conferences. Indeed, there had been some embarrassing times when the American members were in wide disagreement. In September and December of 1928, three U.S. radiological societies, the American Medical Association and several x-ray equipment manufacturers agreed to the establishment of a protection committee. This was called the U.S. Advisory Committee on X-ray and Radium Protection. It got started in 1929. L. S. Taylor was elected chairman, partly because he was the American representative to the international committee, and partly because he was a “natural” for the job. Since his home base was the National Bureau of Standards (NBS), the Bureau agreed to commit some resources to its management. Like many temporary arrangements, it turned out that the Bureau was host for over two decades. Most of the earlier reports were issued as NBS Handbooks. Again, its early concerns involved mostly external radiation sources. The committee did not meet between the end of 1941 and 1946. Its members also served on a voluntary basis.

2. NCRP and ICRP in the Early Postwar Years

In 1946, the American Advisory Committee assembled to revise NBS Handbook 20 on “X-ray Protection.” Instead, they decided that a reorganization was needed. The membership needed to be broadened to include all U.S. organizations interested in radiation protection. (These are enumerated by Taylor, 1979, p. 7-005.) At this time, the name was changed to National Committee on

Radiation Protection. Subcommittees were added to the structure; this including a subcommittee (Subcommittee-2) on Permissible Internal Dose chaired by K. Z. Morgan from Oak Ridge. The only other subcommittee concerned primarily with radioisotopes was Subcommittee-6, which was chaired by H. M. Parker from Hanford. It considered the handling and disposal of radioactive isotopes, including the fission products. The first meeting of Subcommittee-2 occurred in September 1947.

In all of these years, neither NCRP nor the Bureau of Standards had any statutory responsibility for radiation protection.

The International Commission on Radiological Protection (replacement for International Committee) got going somewhat later after the end of the war. There was preliminary work in several countries, particularly in the United Kingdom. The first postwar meeting occurred in 1950 in conjunction with the Sixth International Congress of Radiology. It was only one day long. Nevertheless, some recommendations were posed, none of them concerning radionuclides, except to indicate that values for "internal radiation" would appear later. Subcommittees were designated, essentially identical in subject matter to those of NCRP. The first Tri-Partite Conference (section 4) had already been under way, and there was some mixing of ICRP and Tri-Partite members, especially for the second Tri-Partite meeting, which was held in England. By this time, internal dose was a lively topic in ICRP, but it was NCRP that had led the way initially, along with the Tri-Partite conferences.

3. NCRP and ICRP in Later Decades

In 1964, the NCRP became a U.S. Congressional Charter Organization under Public Law 88-376. Its name was changed to *National Council on Radiation Protection and Measurements*. This came about because of the increasing awkwardness of having it "sponsored," even informally, by NBS while it was not a governmental organization. Also, development of the Federal Radiation Council (FRC) (see section 5) had brought about many problems of interrelationships between the governmental and nongovernmental modes of operation. Under a Congressional charter, the NCRP could be an independent body, free to cooperate at will with ICRP, FRC, ICRU,^(a) et al. The association with the NBS and publication of the reports as NBS Handbooks ceased, although it was an entirely amicable parting.^(b) The various subcommittees of the executive committee became committees. The functions of the former executive committee were assumed by a board of directors. The internal dose problems were concentrated in Committee-2. Many new committees were formed and the parallelism with ICRP began to fade. However, Lauriston S. Taylor continued as president, and, except for a small secretariat, the members served, as before, on a voluntary basis.

In 1968, Committee-2, which had been chaired by K. Z. Morgan from the very beginning, was disbanded. Its functions were replaced by several internal emitter

(a) International Commission on Radiation Units and Measurements.

(b) An interesting side light was the renumbering of all of the issued NBS Handbooks as NCRP reports. Do not be confused by the double numbering seen in some of the references or the NBS numbering on the early ones. Only in retrospect did the earlier reports become "NCRP" reports. This led John Hursh in his excellent review of Report No. 39 (Hursh 1972) to wonder if "the NCRP child was reluctant to acknowledge its NBS father."

committees. There were flaws in that organization—a case of a system where the best of intentions just did not work even though several reports on specific elements were prepared. In 1977, a single committee was again established for internal emitter standards, that had some of the functions of a steering committee.^(a) Much of the work was parceled out to task groups.

There were, and are, other committees and task groups working on aspects of radionuclide behavior, e.g., environmental aspects, waste disposal. A history of some of this work can be seen in the report of Scientific Committee 57 (NCRP 1985a). Rosters of membership are in NCRP annual reports and the compendium by L. S. Taylor (1979).

In the following sections, we will see much of the work of the original Committee-2, since it predominated the period we must consider most closely. However, the results of other committee activities will be mentioned as appropriate.

During these decades, the ICRP changed less than did the NCRP. It remained relatively compact, with a main commission and four committees. Committee-2 continued to be the one chiefly cognizant of internal emitter standards. Committee-4 became involved with practical evaluations of radionuclide contamination, including the environment as well as the work place. There were official observers to ICRP from several international organizations and a number of special task groups were appointed, many of them under Committee-2. We will discuss their work in connection with specific matters. The secretariat was small originally, but has grown. Currently (1985), it is headed by F. D. Sowby at Sutton, Surrey, United Kingdom. The chairman changes every few years. Morgan continued to chair ICRP Committee-2 until J. Vennart succeeded him in 1973.

One major difference in practices between NCRP and ICRP is that the main commission of ICRP is the final decision maker. In NCRP, matters of *basic* radiation protection criteria must go through Committee-1, and any needs for real arbitration go to the board of directors. However, the primary hurdle is that every report must have approval, or at least not be disapproved, by each member of the entire seventy-five member council.^(b) As a result, the NCRP has seldom had to retract a recommendation. On the other hand, the process is frequently a painfully slow one. It has been definitely slow for the internal emitter work. However, recently the NCRP has produced several reports concerning radionuclides that are cited in other chapters and recently a general document (NCRP 1985a) responding for U.S. practices to the concepts contained in ICRP reports 26 and 30 (ICRP 1977, 1979).

4. The Tri-Partite Conferences on Internal Dosimetry

Very soon after the end of World War II, scientists involved with the biomedical problems of radioisotopes felt the need to establish standards for radionuclides on a much more general basis than before. There were also many aspects of external radiation standards that needed work. Representatives of the three countries that had worked most closely together on radionuclides during the war (Canada, the United Kingdom, and the United States) met together, hence the name “Tri-Partite Conferences.” One reason for this selection of

(a) This is NCRP Scientific Committee 57. It is chaired by the author of this book. There are about thirty scientists involved in the committee and its several task groups.

(b) Occasionally, a negative vote has been allowed to stand, but this is unusual.

membership was the perceived need to work with material that had not yet been declassified. These three groups already had liaison established.

There were three conferences:

Chalk River, Ontario, September 29-30, 1949

Buckland House, near AERE, Harwell, United Kingdom, August 4, 5, 6, 1950

Arden House, Harriman, New York, March 30, 31, April 1, 1953.

There was also an informal meeting or two built around other activities. The Chalk River Conference was extraordinary for its breadth and depth of coverage. The attendees had done their homework well. Those participating were:

United Kingdom

Mr. A. C. Chamberlain
Dr. E. F. Edson
Prof. J. S. Mitchell
Dr. G. J. Neary (secretary)

Canada

Dr. A. O. Braaten
Dr. H. Carmichael
Dr. A. J. Cipriani
Dr. G. H. Guest
Dr. G. C. Laurence
Dr. W. B. Lewis
Mr. G. E. McMurtrie (secretary)
Dr. E. Renton

United States

Dr. Austin Brues
Dr. G. O. Failla
Dr. J. G. Hamilton
Dr. L. Hempelmann
Dr. D. E. Hoffman (secretary)
Dr. Wright Langham (secretary)
Dr. K. Z. Morgan
Mr. H. M. Parker
Dr. L. S. Taylor
Dr. Shields Warren
Dr. B. S. Wolf

The names of most of the U.S. delegation members are already familiar from past chapters of this book.

The second conference, at Buckland House near Faringdon, Berks, had a much smaller U.S. representation and a large U.K. representation. They were:

United States

Prof. Robley D. Evans (part-time)
Dr. R. D. Marinelli
Dr. Lauriston Taylor
Dr. Shields Warren

Canada

Dr. A. Cipriani
Dr. G. C. Laurence

United Kingdom

Mr. W. T. Binks (part-time)
Mr. A. C. Chamberlain
Sir John Cockcroft
Dr. E. F. Edson
Dr. A. Glücksmann (part-time)
Dr. L. H. Gray (part-time)
Dr. J. F. Loutit
Dr. W. G. Marley
Prof. W. V. Mayneord (part-time)
Dr. G. J. Neary
Prof. F. W. Spiers (part-time)

The third meeting, at Arden House in Harriman, New York, was, of course, well populated with U.S. delegates. The attendees were:

United Kingdom

Mr. W. Binks
Dr. J. F. Loutit
Dr. W. G. Marley
Prof. J. S. Mitchell

Canada

Dr. J. D. Babbitt
Dr. A. J. Cipriani
Mr. A. K. Longair
Dr. R. Taylor

United States

Dr. A. J. Brues
Dr. J. G. Bugher
Dr. M. Eisenbud
Prof. G. Failla
Dr. J. C. Hamilton
Mr. J. W. Healy
Dr. L. Hempelmann
Dr. W. H. Langham
Dr. L. D. Marinelli
Dr. K. Z. Morgan
Dr. H. H. Plough
Dr. L. S. Taylor
Dr. S. Warren
Dr. F. W. Western

The published record of these conferences was nil until 1984. There were minutes of the Chalk River Conference prepared by each delegation, which differed in emphasis and detail. The two succeeding conferences appear to have more uniform sets of minutes, each carefully marked as containing only the *unclassified* part of the official minutes. These minutes found their way around by personal communications. Mine came from John Hursh, K. Z. Morgan, and L. S. Taylor, to whom I am grateful.

The hiatus in published information concerning these conferences was cleared in 1984 by publication of a full documentation prepared by Lauriston S. Taylor as cited earlier (Taylor 1984). This volume contains not only the minutes referred to above, but many letters and other communications. They include early calculations of standards for drinking water cited in a previous chapter. We owe much to Dr. Taylor for unearthing and collecting this important material and to Bruce Church of the Department of Energy (DOE) for arranging its publication.

These conferences began the system for handling radionuclides used for over two decades as presented in ICRP/NCRP reports. Also "standard man," a lung model, and other important innovations started here. Still more amazing is that the quantum jump occurred at the Chalk River Conference, one of only two days' duration! The others, while important, seemed to be fine-tuning the bold steps taken at the first meeting. It must have been an inspired group and/or one presenting ideas that had been incubating for many years during World War II.

Note that all of this got arranged on an essentially ad hoc basis.

5. The Federal Radiation Council

The FRC was a product of the problems of fallout (chapters 12 and 13). It was officially based in the U.S. government, but it utilized, on an ad hoc basis, a considerable number of talented scientists from numerous laboratories, private and public.

As the ramifications of the fallout controversy spread, more and more agencies of the federal government were drawn in. It was no longer the Atomic Energy Commission (AEC) or even the AEC and the Public Health Service (PHS) (see chapter 12). In 1959, by Public Law 86-373, the FRC was formed "to advise the President with respect to radiation matters, directly or indirectly affecting health, including guidance for all Federal Agencies in the formulation of radiation standards and in the establishment and execution of programs of cooperation with the States . . ." Officially, the council consisted of the Secretaries of the Department of Agriculture; Department of Commerce; Department of Defense; Department of Health, Education and Welfare (HEW); Department of Labor; and the chairman of the AEC. The special assistant to the President for Science and Technology was also included ex officio. A chairman was designated by the President "from time to time" from among the members of the council.

Obviously, these individuals could not do the technical work themselves. Each agency nominated delegates to a Working Group. A secretary of the council was designated from senior staff of a participating agency, usually HEW. A professional secretariat was organized. The Working Group then undertook specific projects by using staff detailed from the member agencies and, as urged by PL 86-373, consultation with qualified scientists in biology and medicine and in the field of health physics, including the president of the National Academy of Sciences (NAS), the chairman of the NCRP, etc. A considerable number of scientists were requested to present data, ideas, and opinions to the council and did so willingly.

Since the work of the council revolved primarily around fallout problems, most of its activities involved radionuclides either directly or by implication. The council issued detailed reports. Summaries were placed in the *Federal Register* as a "Memorandum for the President" according to the statutory responsibility. They contained recommendations over the signature of the chairman of FRC. The *Federal Register* item was always followed by a statement signed by the President, which approved the recommendations "for the guidance of Federal agencies." Thus, the FRC was almost a regulator for the federal establishment. However, we will view it as primarily an advisor, since its recommendations were always in the form of "guides" or some similar appellation.

The council was a very active and effective force. It urged more vigorously than anyone before the importance of evaluating biological risk in comparison to the benefits of a given activity in an overt act of optimization. Its recommendations were directed much more at potential population exposures than those of either ICRP or NCRP at the time. Furthermore, the terminology was altered from "maximum permissible exposure" or "concentration" to "radiation protection guides." The guides for radioisotopes were frequently given in three progressively rising ranges, each of which called for more vigorous action.

Because of problems in the actions of some states in response to contamination from fallout, the FRC found it necessary to develop a separate set of guides called "protective action guides" to apply specifically to action in case of environmental contamination. The substance of these problems and of this development is contained in chapter 12.

In its relatively short existence, the FRC produced eight reports (FRC 1960; FRC 1961; FRC 1962; FRC 1963; FRC 1964a,b; FRC 1965; and FRC 1967). There were also three advisory reports from the NAS (FRC-NAS 1964; FRC-NAS 1966; and FRC-NAS 1968).^(a)

The first two FRC reports emphasized background material. Report No. 1 was very general; Report No. 2 was more concentrated on radioactive materials deposited in the body as a result of their presence in the environment.

Report No. 3 was a preliminary evaluation of radiation doses and possible health effects of the fallout from atmospheric weapons testing through 1961.

Report No. 4 took into account the additional testing by both the USSR and the United States through 1962 and went further into evaluation of the suitability of foodstuffs for human consumption, prediction of future levels of radioactivity, etc.

Report No. 5 developed the background for protective action guides and applied the philosophy to ¹³¹I.

In Report No. 6, the fallout estimates made for 1963 were verified, and revised estimates were made for 1964 and 1965, including global amounts and amounts in total diet and various dietary components.

Report No. 7 presented more background material for the development of action guides and included protective action guides for ⁸⁹Sr, ⁹⁰Sr, and ¹³⁷Cs.

The scientific impact of Reports No. 3, 4, 5, 6, and 7 has been reviewed in the discussion of fallout in chapters 12 and 13. The basic guides in Reports No. 1 and 2 utilized the same key figures as in recommendations of NCRP and ICRP that had already been built into the Code of Federal Regulations. However, there was much emphasis in Report No. 1 on derived guides, such as body and organ

(a) The full titles are given in the reference section.

burden, radioactivity concentration guides, the determination of body burdens, etc. In Report No. 2, the guides were given for ^{131}I , ^{89}Sr , and ^{90}Sr in terms of the three ranges. Range I always included zero.

By the middle 1960s, the problems of the uranium miners on the Colorado Plateau finally received the degree of attention from the federal establishment they should have had earlier (see chapter 3). The FRC helped to organize and took part in several conferences on the subject, some of them international, e.g., the Technical Advisory Conference on Uranium Mines, TACUM. They contracted for yet another advisory report from the NAS, this one on radiation exposure of uranium miners. Even prior to this last advisory report, FRC Report No. 8 appeared. It contained guidance for the control of radiation hazards in uranium mining. Details are in chapter 3, along with the citation.

Unfortunately, the first seven reports issued as staff reports of the FRC do not name the staff, although they occasionally acknowledge advice from individuals. Fortunately, the two NAS advisory committees that contributed to these reports can be named.

Membership of NAS Committee preparing working paper on strontium and cesium (FRC-NAS 1964) (pertinent to FRC Reports No. 2 and 7):

Arthur C. Upton, Chairman	Samuel P. Hicks
Howard L. Andrews	Brian MacMahon
Victor P. Bond	Joseph E. Rall
Cyril L. Comar	Eugene L. Saenger
James F. Crow	Shields Warren

Membership of NAS Committee preparing special report to the FRC on *Pathological Effects of Thyroid Irradiation* (FRC-NAS 1966) (pertinent to FRC Reports No. 2 and 5):

Shields Warren, Chairman	Leo K. Bustad
Subcommittee on Effects of	Cyril L. Comar
Radiation on the Thyroid Gland	Louis H. Hempelmann
Howard L. Andrews	Albert W. Hilberg
Victor P. Bond	

Membership of NAS Committee preparing a special report to the FRC on *Radiation Exposure of Uranium Miners*, (FRC-NAS 1968) (pertinent to FRC Report No. 8):

Cyril L. Comar, Chairman	Averill A. Liebow
Subcommittee on Radiation	Brian MacMahon
Exposure of Uranium Miners	Paul E. Morrow
Howard L. Andrews	Eugene L. Saenger
Victor P. Bond	Shields Warren
George W. Casarett	

Throughout, there was a standing advisory committee of the NAS to the FRC. The members were:

C. L. Comar (Chairman), Cornell University
 S. Abrahamson, University of Wisconsin
 H. L. Andrews, Puerto Rico Nuclear Center
 (Formerly at National Institutes of Health)
 V. P. Bond, Brookhaven National Laboratory
 G. W. Casarett, University of Rochester

L. H. Hempelmann, University of Rochester
S. P. Hicks, University of Michigan
B. MacMahon, Harvard School of Public Health
J. E. Rall, National Institutes of Health
W. L. Russell, Oak Ridge National Laboratory
E. L. Saenger, University of Cincinnati
S. Warren, New England Deaconess Hospital

Fortunately, the eighth and final report gives full details of staff as well as the Working Group and all of the NAS Advisory Committee and panels. Those not listed earlier are given below:

Federal Radiation Council

Members

Secretary of Health, Education and Welfare (Chairman)
Secretary of Agriculture
Secretary of Commerce
Secretary of Defense
Secretary of Labor
Chairman, Atomic Energy Commission
Special Assistant to the President for Science and Technology (Adviser)

Staff

P. C. Tompkins, Executive Director
C. C. Palmiter, Special Assistant

Working Group

H. N. Doyle, Department of Health, Education and Welfare
G. M. Dunning, Atomic Energy Commission
W. Mann, Department of Commerce
H. B. Mitchell, Department of Defense
J. P. O'Neill, Department of Labor
A. B. Park, Department of Agriculture
R. G. Stott, Department of the Interior
J. G. Terril, Jr., Department of Health, Education and Welfare
E. C. Van Blarcom, Atomic Energy Commission
F. Western, Atomic Energy Commission

Ad hoc panels of the NAS in addition to those named and to the standing Advisory Committee to FRC are:

Ad Hoc Panel

Mining Practice and Economic Factors

E. C. Van Blarcom (Chairman), Atomic Energy Commission
H. N. Doyle, U.S. Public Health Service
R. D. Evans, Massachusetts Institute of Technology
G. A. Franz, Jr., Colorado Bureau of Mines
D. A. Holaday, U.S. Public Health Service
C. R. Jensen, New Mexico Department of Public Health
J. P. O'Neill, Department of Labor
J. T. Sherman, Atomic Industrial Forum, Inc.
R. G. Stott, U.S. Bureau of Mines
J. Westfield, U.S. Bureau of Mines

Epidemiology

A. W. Hilberg (Chairman), U.S. Public Health Service
V. E. Archer, U.S. Public Health Service
M. A. Connell, Grants Clinic (Grants, New Mexico)

F. E. Lundin, Jr., U.S. Public Health Service
 D. A. Morken, University of Rochester
 H. M. Parker, Battelle, Pacific Northwest Laboratories
 G. Saccomanno, St. Mary's Hospital (Grand Junction, Colorado)
 R. Seltser, The Johns Hopkins University
 B. O. Stuart, Battelle, Pacific Northwest Laboratories
 J. K. Wagoner, Harvard School of Public Health

Review of Dosimetry and Biological Models

H. M. Parker, Battelle-Northwest, Pacific Northwest Laboratory

When the Environmental Protection Agency (EPA) was created in 1970, the functions of the FRC were assimilated into the EPA Office of Radiation Programs. The EPA organized an advisory committee (The Radiation Exposure Advisory Committee, REHAC), which functioned for a while. It was chaired by Roger McClellan, Lovelace Foundation. Later, general reductions in federal funding led to dissolution of this and many other advisory committees. The EPA operated in a different mode anyway and made much more use of the statutory public hearing mechanism than the old system of advisors and advisory committees. Some excellent hearings were conducted. We have had occasion to cite these in earlier chapters and will describe briefly the EPA's general role in standard setting for radionuclides in a later section.

During the administration of President Carter, as part of a review of radiobiological knowledge, the need was voiced to have again multiagency input into the standard-setting process. An attempt was made to devise an organization patterned after the FRC. It even reached the *Federal Register* in February 1980 under the title "Radiation Policy Council." However, the budget cuts of the early 1980s did not allow any such expansion.^(a)

We have examined the general contributions of the FRC in some detail because they are not as well known or as easily found as some of the other enterprises we have examined. A general description of their mode of operation is seen in section III G. Specifics are quoted in the pertinent chapters.

Many of the ideas and most of the limits recommended by FRC are still in use in one way or another; some have never been rescinded. Also, the FRC's influence has been continued by virtue of frequent quotation. It had an important influence in the radioisotope field by pioneering work on many of the environmental problems and procedures we now consider commonplace, and in unifying the activities of the federal establishment to the extent possible.

6. The U.S. Public Health Service's Bureau of Radiological Health, National Advisory Committee on Radiation

Throughout earlier chapters, we have seen specific contributions of the U.S. PHS both by their personnel and as an organization (see chapter 3 on uranium miners and chapters 12 and 13 on fallout problems). There was, of course, much research support, both extramural and intramural, at the National Institutes of Health, most of which concerned basic radiobiology.

(a) After the cutoff date for this chapter, another federal group was organized around these same problems—the Committee on Interagency Radiation Research and Policy Coordination (CIRRPC). It seems to be making some progress.

In a development that we can only mention, the HEW, via the PHS, entered in 1958 the arena of population exposures as well as instrumentation and methodology, first by sponsorship of a laboratory in Cincinnati and later a division, soon renamed Bureau of Radiological Health with satellite laboratories. This group did not dip very far into standard setting per se. They did do invaluable work in the field of assessment, particularly around the problems of fallout, in epidemiology of direct bearing on the verification of standards, in developing methodologies, and in fostering education and training.^(a) For many years, the Bureau of Radiological Health had an advisory committee, chaired by Russell Morgan, professor of Radiology at The Johns Hopkins University, that served some of the same functions as the NAS advisory committee to the FRC. This group, called the National Advisory Committee on Radiation (NACOR), got caught up in some of the controversies surrounding fallout, population exposures in general, and the basic impact of all uses of radiation on the public health. This included medical and commercial applications. NACOR issued several reports calling attention to needs for radiation protection. Members of this committee during the 1960s included:

Russell H. Morgan, The Johns Hopkins Medical School, Chairman
 John H. Barr, Tufts University
 Victor P. Bond, Brookhaven National Laboratory
 Richard H. Chamberlain, University of Pennsylvania Hospital
 Cyril L. Comar, Cornell University
 James F. Crow, University of Wisconsin
 Ralph E. Dwork, Ohio State Department of Health
 Howard C. Eberline, Eberline Instrument Corporation
 Alexander Grendon, University of California
 Herman E. Hilleboe, New York State Department of Health
 Leon O. Jacobson, Argonne Cancer Research Hospital
 Hardin B. Jones, University of California
 Roscoe P. Kandle, New Jersey State Department of Health
 Edward B. Lewis, California Institute of Technology
 Berwyn F. Mattison, American Public Health Association
 Russell I. Pierce, U.S. Public Health Service
 Blucher A. Poole, Indiana State Board of Health
 Laurence L. Robbins, Massachusetts General Hospital
 William J. Schull, University of Michigan
 Wendell G. Scott, Washington University
 J. Newell Stannard, University of Rochester
 Lauriston S. Taylor, National Bureau of Standards
 George W. Thorn, Peter Bent Brigham Hospital
 Arthur C. Upton, Oak Ridge National Laboratory
 Abel Wolman, The Johns Hopkins University
 Arthur H. Wuehrmann, University of Alabama

7. The U.S. National Academy of Sciences-National Research Council

We have already seen the frequency with which the academy was consulted by federal agencies and have seen some of the advisory committees that were appointed. During the height of the fallout events, the academy was requested to provide technical information to both the scientific community and the

(a) Many of the environmental functions of the Bureau went to EPA in 1970. The others remained, partly under the auspices of the Food and Drug Administration.

general public on all aspects of radiation usage and effects. This began in 1956. Detlev Bronk, who was president of the Rockefeller Institute in New York at the time, but had spent much time with the academy, lifted the proceedings completely out of the governmental arena by arranging financial support from the Rockefeller Foundation. The work began in 1955, and summary reports were issued in 1956.^(a) They bore only obliquely on standards.

In 1960, a series of reports was issued covering all aspects of the Biological Effects of Atomic Radiation, known as the "BEAR" reports and authored by the "BEAR" Committees. There were six basic areas, each represented by a committee: genetic aspects, agriculture and food supplies, meteorological aspects, disposal and dispersal of radioactive wastes, oceanography and fisheries, and pathologic effects. The only ones of direct concern to the radionuclide standards field were subcommittees of the Committee on Pathologic Effects. These were as follows:

Subcommittee on Internal Emitters

Austin M. Brues, Argonne National Laboratory, Chairman
 Thomas F. Dougherty, University of Utah
 Miriam P. Finkel, Argonne National Laboratory
 Hymer L. Friedell, Case Western Reserve University
 Wright H. Langham, Los Alamos Scientific Laboratory
 Kermit H. Larson, University of California at Los Angeles
 Herman Lisco, Argonne National Laboratory
 William P. Norris, Argonne National Laboratory
 J. Newell Stannard, University of Rochester
 Joseph D. Teresi, U.S. Naval Radiological Defense Laboratory, San Francisco
 Roy C. Thompson, General Electric Company, Richland, Washington
 Raymond E. Zirkle, University of Chicago

Subcommittee on Inhalation Hazards^(b)

Harry A. Kornberg, General Electric Company, Richland, Washington, Chairman
 W. J. Bair, General Electric Company, Richland, Washington
 Stanton H. Cohn, Brookhaven National Laboratory
 C. C. Gamertsfelder, General Electric Company, Cincinnati
 J. W. Healy, General Electric Company, Richland, Washington
 Francis R. Holden, Radiation Detection Company, Palo Alto
 James K. Scott, University of Rochester
 J. Newell Stannard, University of Rochester
 George V. Taplin, University of California Medical Center, Los Angeles

These reports did address directly the adequacy of standards. They also contributed indirectly by addressing research needs. All were oriented toward the evaluation of hazards. The pertinent reports, for our purposes, are referenced in chapters 9 and 13 and by Bell (1977).

As the fallout furor decreased, the BEAR committees were disbanded. However, the growing concern over the effects of very low levels of ionizing radiation on populations led to new requests to the National Academy of Sciences-National Research Council (NAS-NRC). These committees (funded by the EPA) began work in the early 1970s. Their reports were known as "BEIR"

(a) All of these are listed by Bell (1977). They covered the waterfront from radiobiology through transportation to waste disposal.

(b) A photograph of the Inhalation Hazards Subcommittee taken at one of its meetings is shown as figure 16.1.



FIGURE 16.1. Photograph of the Subcommittee on Inhalation Hazards of the National Academy of Sciences–National Research Council BEAR Committee taken in the early 1960s. Seated from left to right: W. J. Bair, F. R. Holden, H. A. Kornberg, J. K. Scott, J. W. Healy and standing: S. H. Cohn and J. N. Stannard. Note: Despite diligent efforts, we have been unable to identify the lady to Mr. Healy's left. (Photo courtesy of Pacific Northwest Laboratory.)

reports for “Biological Effects of Ionizing Radiation” and the committees as the “BEIR” committees. The first and third have been quoted liberally in previous chapters and will be later in this one. The second report concerns primarily benefit-cost relationships in the radiation field.

BEIR reports I and III have addressed specifically the assessment of risk to man from low-level exposures to ionizing radiation. Since the standard-setting process is moving more and more to a risk-based system, these reports have had much use by those concerned with setting standards for radioisotopes. Unfortunately, the unknowns have grown with consideration of lower and lower levels. The committee responsible for the third report could not agree on some basic aspects of the dose-response relationship to be applied to the limitation of exposure at very low levels. The result was a majority and a minority report and the promise of further controversy ahead.

A new committee (BEIR IV-alpha), organized in 1985, is the first to deal specifically with radionuclides, in this case, alpha-emitting radionuclides.^(a)

(a) Note added in proof: Its report (BEIR IV) has just been issued (January 1988). It concentrates on radon problems, including a re-examination of the epidemiology discussed in chapter 3 (NAS-NRC 1988).

8. The Congress of the United States

To the extent that the Congress advises everyone by its control of appropriations, it is always present in work such as we are discussing. However, there are two specific aspects of importance to our current topic.

The Joint Committee on Atomic Energy, one of the best features of the Atomic Energy Act, sponsored many hearings that brought scientists from the laboratory and industry together with administrators, regulators, and law makers around problems of the adequacy of our present standards for radiation exposure and our knowledge of radiobiological effects. The transcripts provide an invaluable resource, as we have seen (e.g., Congressional hearings 1963).

The U.S. Congress also had an influence on the whole process of standard setting and evaluation by its passage of the National Environmental Protection Act (NEPA) in 1970. In this they were behaving more as regulators than advisors. Hence, this activity will be reserved for section II B.

9. The Professional Societies

The radiological societies very early developed ways to have input to the practices of radiation protection. Many had formal committees on the subject. Of most pertinence to standards for radionuclides are the activities of the Standards Committee of the Health Physics Society and of the American Nuclear Society. In addition to general matters, these committees have contributed, even worked in close collaboration with, federal groups to devise methodologies and philosophies for assessment, e.g., in bioassay for radionuclides.

10. Other Activities

The above concerns primarily the United States, except for the discussion of the ICRP. Each country has had its own way of implementing the general recommendations from groups such as the ICRP. Also, each has ways of evaluating performance and focusing new knowledge. A good example is the U.K. National Radiological Protection Board (NRPB).

For the same reasons as lay behind the organization of BEAR, BEIR, and the FRC, the United Nations developed a Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) in 1955. Since then, UNSCEAR has reported yearly to the General Assembly and produced comprehensive reports at irregular intervals: 1958, 1962, 1964, 1966, 1969, 1972, 1977, and 1982. The work was carried out through meetings of specialized scientists, preparation of working papers, and a small scientific staff. These reports primarily evaluate current information and any changes occurring since the previous report. They do not overtly enter the arena of standard setting, but the information is so complete, so authoritative, and so pertinent that it has had much influence on any conclusions regarding risk estimation, dose-response relationships, source terms, etc. They are very complete source books on radionuclides in the environment, both natural and manmade, assessment of doses therefrom, and possible effects.^(a)

The reports themselves are relatively brief, but the appendices are voluminous. The two most recent UNSCEAR reports (UNSCEAR 1977, 1982) are cited

(a) The authors of these comprehensive reviews did not find reasons for significant changes in the basic standards underlying radiation protection.

for convenience in the bibliography. Through these, the reader can explore earlier reports.^(a)

B. The Regulators

It is not our purpose or need to review the development of regulations. We do need to consider the uses made by regulating bodies of the research data developed at such cost in money and careers.

1. The U.S. Atomic Energy Commission

The AEC was the first major regulator^(b) for radioisotopes. The major documents appeared as parts of the U.S. Code of Federal Regulations. They were primarily directed at the large contractors of the AEC and, as the program for peaceful uses of atomic energy grew, at the licensees also.

The regulators in the AEC days did not agonize so much over the basic permissible levels as they did over quantitative behavior of radioisotopes in and around the various installations and their excretion by man. The Code of Federal Regulations Part 20^(c) utilized primarily the NCRP/ICRP 1959 recommended values to construct a large table of maximum permissible concentrations (MPC). They added a second set of values for exposures of the general population (see section IV D).

When the problems of the movement of radionuclides through the environment became paramount, the AEC found it necessary to revise the MPC values for certain radionuclides. For example, the value for iodine was reduced by a factor of seven hundred because of concentration in the food-milk chain (see chapter 15). This applied to light-water-cooled reactors. This and other changes have appeared in Appendix I and elsewhere. As the levels in Appendix I have been lowered, standards for radionuclides have become more and more likely to control operations.

2. The U.S. Nuclear Regulatory Commission

When the AEC was disbanded in the mid-1970s, its regulatory functions went to the Nuclear Regulatory Commission (NRC) for the large sources and to the Food and Drug Administration (FDA) for items like medical radionuclides. The basic criteria did not change markedly, nor did the Code of Federal Regulations. The modifications came out principally as "Regulatory Guides," which covered nearly every aspect of operating or building nuclear energy installations. There were some interim changes in basic levels. Now, however, a thorough reworking of the Code of Federal Regulations is under way. The NRC is keeping in close touch with all groups working on revisions of radionuclide standards, and vice versa.

(a) Still another report was issued while this book was in proof.

(b) The MED was, strictly speaking, first, but this was self-regulation within a tightly circumscribed group.

(c) There are over 70 Parts to Title 10 of the Code of Federal Regulations. Most of them concern practical and operational aspects.

3. The U.S. Environmental Protection Agency

Technically, the EPA has jurisdiction over any and all releases to the environment. Details of the management and construction of large nuclear installations are the province of the NRC. Many of the medical and research radioisotopes, both preparation and use, come under the FDA.^(a) However, this is delegation of details. Ultimate responsibility for environmental standards resides in the EPA.

The EPA has much interest in standards for ambient air and for drinking water (chapter 15). Some very fine scientists and a competent NAS committee helped EPA develop a basic document on Quality Criteria for water (EPA 1976), which formed the basis for judgment in EPA and state programs associated with water quality. In the radioisotope field, the EPA seems to have been and to be concentrating on standards for drinking water (as we saw in chapter 15). There have been many hearings and proposals made in the *Federal Register*. The procedure includes developing a "criteria document" that analyzes the information available and theoretically leads inexorably to conclusions regarding suitable concentrations of radioisotopes in drinking water. In the terms we will use later in this chapter, their approach is the *direct* one rather than a computational approach. The EPA thus far has tackled primarily important naturally occurring radionuclides such as radium and uranium (chapter 15).

The standards derived by these analyses are, in general, far lower than any previous recommendations. Many groups over the years have examined the data and concluded that there is basically no evidence requiring drastic reductions of the permitted concentrations. Nevertheless, the EPA seems to be listening to a different drummer and can draw quite different conclusions from the same data. This is partly because they felt it advisable to parcel out the risks from different activities. Naturally, these proposed levels encountered opposition from states and local communities, particularly since some of the proposed levels would require expensive treatment of water supplies that have been serving a given community for generations.^(b)

Obviously, the current controversy surrounding the true picture at low levels of radiation (see chapter 21) leads many to support an ultraconservative view. Since the chances of measuring any biological effects at these low levels, even with the very best of epidemiologic studies, is vanishingly small, the final decisions will probably rest more upon economic and social aspects than upon biomedical information. As potential biomedical effects of *routine operations* are analyzed and found to be quite small, the decision rests more and more on the former.

Since details of the current EPA proposals and the arguments pro and con are far beyond the cutoff point of this history, and we are not reviewing all recommendations anyway (except for chapter 15), we will let the discussion rest at this point except to quote a bit of philosophy from the letter foreword to *Quality Criteria for Water* written by E. C. Beck, Deputy EPA Administrator at the time: "It must be emphasized that national criteria can never be developed to meet

(a) There is little information on what use the FDA makes of the accumulated information bearing on standards.

(b) These are not "enhanced" supplies with contaminants introduced by the activities of man. Treatment of them is not questioned so much.

the individual needs of each of the Nation's waterways —the natural variability within the aquatic ecosystem can never be identified with a single numerical value." (EPA 1976)

4. The U.S. Congress, the Environmental Impact Statement

The Congress became a regulator of radioisotope exposure in the later 1960s. The Baltimore Gas and Electric Company planned to build a nuclear power station at Calder Cliffs on Chesapeake Bay. There was much opposition from various local and national groups. The AEC, which had the licensing authority in those days, declared the plan safe. There was enough agitation, however, to move Congress into action. By passage of the National Environmental Policy Act in 1970, the Congress imposed a much more detailed examination of all aspects of the plan, especially environmental aspects, upon a federal agency, the AEC. This was indeed a landmark decision. It applied to any and all activities with potentially significant environmental impact, not just sources of ionizing radiation.

Thus was generated the *Environmental Impact Statement* (EIS). Among other things, this and other analyses in the radioisotope field showed that solid or potentially solid radionuclides were probably the most important potential radioactive contaminants of the environment, and some attention was drawn away from the noble gases.

The statement required even more detailed ecological investigations *prior* to construction than the fairly stringent AEC regulations. Also, statements were required on much more than the radiological impact, e.g., economic, sociologic, and other impacts.

In the ensuing years, thousands of pages have gone into EISs for each planned or active nuclear installation, as well as thousands of other developments.^(a) These were filled with calculations for the behavior of radionuclides in the plant and in the environment of the specific site. They entailed expenditure of thousands of man-hours by good people. In general, state-of-the-art knowledge was used, and it did not differ fundamentally from the basic criteria we will discuss in this chapter. Indeed, not long after the NRC became the recipient of such statements, guidelines for their preparation were set up that discouraged application of any marked originality by anyone hoping to be licensed in a finite time!

The submission of an EIS was usually followed by a hearing or hearings. The statements themselves and the transcripts of the hearings are a gold mine of information, much of it applicable to the standard-setting process. Perusal of these gives a cross section of what was on people's minds at various points along the way.

It is most unfortunate that these documents are not readily available and that they have not been combed in a scholarly manner to extract the essence of the thinking involved. They are much too ponderous and site specific as they stand. Unfortunate, too, is the fact that once a license was granted the all-important statement was put in a file or even discarded.

(a) This activity was large enough to become the subject of a "handbook" written by Cheremisinoff and Morresi (1977 with fourth printing in 1980). It lists almost thirty areas of concern for the preparation of an EIS and gives examples from air quality to waste disposal. Nuclear facilities are included but are not as major a participant as the furor might predict.

For the purposes of this chapter, we can only say that ideas, especially regarding environmental transport, gradually evolved through these statements. This may be the chief *scientific* contribution of the EIS.

Probably the Congress benefited the standard-setting process for radionuclides by starting this activity. However, it now seems there could have been an easier way.

5. The States

Traditionally in the United States, matters of worker health have been the responsibility of the states. Traditionally also, the PHS has stood ready to provide information and assistance to the states, but it never intruded. Exposure standards to chemical toxicants were set largely by industry and professional societies or groups like the American Council of Governmental Industrial Hygienists.

In the nuclear energy field, the secrecy of the MED and the provisions of the Atomic Energy Act took much of this responsibility away from the states. This included responsibility for radionuclides. Only in the case of naturally occurring radioisotopes was there some of the old system. We saw in chapter 3 how this dichotomy worked against the health of the uranium miners.

Yet, the states generally have excellent departments of health and of labor, and they prepare codes for industries within their borders. In general, these codes have been patterned after the federal codes. In fact, some of the people involved in standard setting at the federal level were called in to advise their home state in the development of codes.

There have been a few instances where a state decided to apply stricter codes than promulgated by, for example, the AEC. An example of this occurred in Minnesota in 1967 to 1969.^(a) The Northern States Power Company wished to construct two large nuclear reactors on the Mississippi River near Monticello, Minnesota. The Minnesota Pollution Control Agency (MPCA) was given powers by the governor to regulate discharges from nuclear power plants. After many hearings and consultations, the permissible discharge level was set lower than those promulgated by either the AEC or the FRC. This was partly on the theory that the Mississippi River acted as a drinking water supply for hundreds of towns downstream and many reactors were being planned on its banks. The action touched off a nationwide controversy and a suit from the Power Company against the MPCA. In its midst, the University of Minnesota sponsored a symposium, "Nuclear Power and the Public," (Foreman 1970) which brought together people from a variety of disciplines and a variety of backgrounds. The central theme was evaluation of health hazards to the public from nuclear reactors, but of almost as much importance was the "preemption" of state regulatory responsibilities regarding releases of radionuclides from nuclear power plants by the federal establishment. Throughout the symposium proceedings, there are allusions to the basic knowledge needed for the standard-setting process, e.g., Auerbach (1970), Commoner (1970), Eisenbud (1970), and Stannard (1970). There were also penetrating general discussions of energy policy.

A similar symposium with the same title was held at the University of Wisconsin some months later.

(a) We saw the consequences of state actions regarding fallout in chapter 12.

As we all know, the states did not have unique information to put into their standard-setting process, only unique points of view. In the case of nuclear power plants, the federal guidance prevailed.

There may be another polemic developing. In this one, the states want *higher* permitted levels than the federal proposals. Many of the states are balking at the proposed drinking water standards for radioisotopes coming from EPA (chapter 15). They are using the same basic data but finding no biomedical reason to go so low and no economic benefit in having to treat water supplies unnecessarily (Hazle 1982). A further aspect is the fact that the analytical laboratories of the cognizant departments of the states are now quite competent. Sometimes they do not get the same answers as the EPA for current concentrations of naturally occurring radionuclides in a given water supply.

If pressures increase toward ever lower radioisotope concentrations in water or air, there are conflicts with states, even with municipalities, ahead. One reason is that the states see areas in the chemical toxicity realm where action and resources are more needed. As a result, many of the individuals with expertise in the radioisotope field are finding a need to learn about the standard-setting process for chemical toxicants.

So much for the organizations involved. Let us now consider the uses of the research data in standard setting.

III. Direct Derivation of Standards for Radionuclides

In the field of industrial hygiene and toxicology, it has been common practice, especially in the decades before organizations like National Institute of Occupational Safety and Health, Occupational Safety and Health Administration, etc., to develop standards on the basis of in-plant experience. This usually meant that the development of symptoms and of overt injury called attention to the presence of a problem. In retrospect the concentrations of the noxious agent in areas where cases of injury developed were compared with those in "safe" areas. A standard was developed, frequently with the interposition of a safety factor and the assumption of a threshold dose or concentration below which no effect would be expected. The early standards for protection from x rays and the gamma emissions from ^{226}Ra used this same approach, viz., determination of a safe level and the doses therein. We will term this use of information in retrospect "direct determination of standards."

The first standard for a radionuclide was developed by the direct method, although in somewhat modified form since the measurements were of body burden rather than air concentrations. This is the bench-mark figure for ^{226}Ra .

A. The Radium-226 Standard

The general characteristics of ^{226}Ra and the experience, both research and clinical, with the dial painters, radium chemists, radium patients, and others have been detailed in chapter 1. The story of how the research data were used to develop the first standard for a radionuclide has been told graphically on several occasions, especially by Robley Evans. His most readily available review is from the Health Physics Society Silver Anniversary Symposium (Evans 1981). The Kathren-Ziemer volume contains another summary by Evans, which places greater emphasis on instrumentation and methodology (Evans 1980).

The circumstances for development of this first standard were somewhat unusual. The saga of the dial painters had unfolded, and new information was coming in regularly, particularly from and to the Massachusetts Institute of Technology (MIT) group. When U.S. entry into World War II looked all but inevitable, the U.S. military establishment became engaged in production of large numbers of radium-dial instruments. The U.S. Navy took the lead in assuring that the dial-painting experiences of World War I would not be repeated. Evans reports that a Captain C. Stephenson visited his laboratory at MIT in 1940. He urged that they provide safety standards for radium and luminous paint. Indeed, if such standards were not forthcoming in a reasonable time, Evans would be inducted into the Navy and assigned to production of standards! Evans did not need prodding of this magnitude, but it helped overcome some of the inevitable inertia of getting some sort of consensus from those concerned.

In view of the stated needs, an advisory committee was established under the Advisory Committee on X-Ray and Radium Protection of the NBS (see section II) to develop materials on the safe handling of radioactive luminous compounds. As Evans (1981) describes the events, a decision regarding the maximum permissible body burden for ^{226}Ra was arrived at on the basis of experience with twenty-seven persons who had been studied in depth:

By February 1941 we had a total of some 27 persons with accurately measured body burdens, all of whom had been measured at MIT or in New Jersey with MIT apparatus. We had observed 7 persons with residual body burdens below $0.5\ \mu\text{Ci}$ and no injuries, whereas some 20 persons with residual burdens of $1.2\text{--}23\ \mu\text{Ci}$ showed various degrees of injury.

After reviewing these 27 cases, and noting that we were obliged to make an "informed judgment" decision, I suggested that we should set the "tolerance level" for residual radium burden in radium-dial painters at such a level that we would feel perfectly comfortable if our own wife or daughter were the subject. I then asked each of the other 8 committee-men individually in turn if he would be content with $0.1\ \mu\text{Ci}$. Unanimously, we all were.

Thus $0.1\ \mu\text{Ci}$ of ^{226}Ra residual body burden was adopted in NBS Handbook 27 which was issued 2 May 1941, some 7 months before Pearl Harbor, 2 months after the then-secret discovery of plutonium, and 18 months prior to the first demonstration of a nuclear reactor.

(From Evans 1981, pp. 442-443)

So the first standard for a radioisotope came directly from data on and experience in humans.^(a,b) It was published as NBS Handbook H-27 (1941). The sequel and the fact that a large factor of safety was involved can be seen also in Evans's remarks:

- (a) It might be remarked that the criterion of considering the "tolerance level" in terms of one's own wife or daughter indicates that chivalry was still alive in 1941.
- (b) The decision makers were: L. F. Curtiss, National Bureau of Standards (chairman); R. D. Evans, physicist, MIT; G. Failla, physicist, Memorial Hospital, New York; F. B. Flinn, industrial hygienist, Columbia University; H. S. Martland, physician, medical examiner of Essex County, New Jersey; J. E. Paul, Radium Corporation of America, New York; J. S. Rogers, U.S. Department of Labor; Capt. Charles S. Stephenson, physician, Bureau of Medicine and Surgery, U.S. Navy; Col. G. T. Taylor, Radium Chemical Company, New York. Note that the instigator and advocate, Capt. Stephenson, was folded into the decision-making process!

After World War II, NBS Handbook 27 was designated as NCRP Report 5, and also the ICRP adopted the 0.1 μCi permissible burden. Now, 39 yrs later, and with more than 2000 radium patients studied at MIT, New Jersey, the Argonne Cancer Research Hospital and the ANL Center for Human Radiobiology, no exception has been found to the 0.1 μCi residual radium standard as an innocuous body burden.

The 0.1 μCi Ra bench mark was based on the residual body burden of patients, long after they had acquired a much larger initial burden, commonly the order of 100 times larger. When used as a radiation protection guide the 0.1- μCi bench mark represents not a residual burden but the maximum body burden reached during intake. Thus there is a substantial additional safety factor of between 1 and 2 orders of magnitude built into the conventional use of the 0.1 μCi Ra standard as a maximum body burden rather than as a residual body burden evaluated many years after exposure. (From Evans 1981, p. 443)

This standard has withstood constant reevaluation as more and more data have accumulated (Evans 1967b, and numerous works cited in chapter 1 as well as the 1981 summary). This includes current work under way at Argonne National Laboratory (ANL).

Further along, Evans discusses the appearance of eye lesions from radium in the beagle dog (see chapter 1) and the marked difference in apparent sensitivity of rodents compared to man for a large number of substances. In the early MIT work with rats (see chapter 1), to produce a crop of tumors, the Wistar rat required a skeletal concentration of radium far above that known to produce bone cancers in man. This led to Evans's well-known dictum, reiterating Pope's: "The proper subject for the study of man is man."

We will see examples in subsequent sections of how this dictum can be applied without engaging in experimental effects work in humans. That would be unthinkable.

Meanwhile, it is interesting to note that the data on ^{226}Ra from the large beagle dog experiments described in earlier chapters of this book have been shown to contribute significantly to evaluating the dose-response relationship in humans. Work by Otto Raabe and colleagues at the University of California at Davis (Raabe, Book, and Parks 1980) correlates the response ratios with the normal life expectancies of mice, dogs, and humans. The correlation was good and brings the beagle data in sight of direct application to standards rather than through the toxicity ratio procedure which we discussed in chapters 7 and 8. Further, the University of California at Davis group (Raabe, Parks, and Book 1981) described dose-response relationships for bone tumors in beagles exposed to ^{226}Ra and ^{90}Sr based on lifetime experiments and compared them with those for mice and men. They found a marked effect of dose rate with a much smaller average cumulative radiation dose to death for those individuals that died of bone cancer at low dose rates, i.e., small body burdens. The dictum that the proper subject for the study of man is man was reiterated in the University of California at Davis work. Mice required only one-tenth as long and dogs only about one-third as long to develop bone tumors at a given dose rate as people. The response ratios correlated well with normal life expectancies.

As if in response to the admonition to stick with people, the group at the Center for Human Radiobiology developed a comprehensive summary of the dose response for production of bone sarcomas in female radium-dial painters. The work was presented at the International Conference on the Radiobiology of Radium and the Actinides held at Lake Geneva, Wisconsin, in October 1981. Here Rowland, Stehney, and Lucas (1983) drew generalized dose-response functions from a population of 3,055 women identified as having been dial

painters at one time or another. There were two subpopulations, one based upon year of entry into the industry and the other upon date of first measurement. Dose-response functions consistent with ideas developed from much earlier work could be fitted to the data. Risks could be derived directly from these dose-response functions.

While the entire story is much more sophisticated now than in 1941, the results in no wise counter in any serious way the validity of the standard then based on approximately a hundred times fewer people.

B. Standard for Radon-222

The basic dosimetric and biomedical problems associated with the first decay product of ^{226}Ra (^{222}Rn) and of its subsequent daughter products and their historical development were traced in chapter 3. Only a little was said there about the derivation of the original standards for radon. We will repeat in part and expand here on what was said there.

The standard for radon presents another example of one generated directly from the data on humans. This time it depended largely on measurements of the exposure environment, since the short half-life of radon and its immediate progeny meant that residual body burdens were usually too low to infer much about initial tissue contents^(a) from excreta measurements and the like. The derivation was much like the classic procedures of industrial hygiene.

Evans and coworkers played an active part in the development of the first radon standard as they did in development of the ^{226}Ra standard. It was based upon measurements of air concentrations of both radon and thoron and represents one of the earliest permissible levels established for radioactive aerosols.

The genesis of the work was the concern of an insurance carrier for a large gas mantle manufacturing company. As described in chapter 4, thorium compounds are used in the manufacture of such mantles, and airborne thorium and thoron were constantly present. The insurance carrier wished an evaluation of the potential health hazards of thoron in these factories. Evans and his colleague, Clark Goodman, at MIT, developed equipment for collecting, in the field, the second daughter product of thoron (thorium B = ^{212}Pb) and sending samples back to MIT for counting. This work demonstrated as early as 1937 the presence of large quantities of thoron in some of the thorium mantle factories (maximum of 4,000 pCi Tn/l; 230 to 4,000 pCi/l range).

Because of the many parallels, it was easy to extend the thinking and the measurements to radon gas. In a classic paper received for publication in 1939 but not published until 1940, Evans and Goodman considered both thoron and radon (although the paper title mentions only thoron) and suggested a safe working concentration for both radon and thoron for plants, laboratories, and offices (Evans and Goodman 1940 and 1980). They started with observations made by Barker in 1934, which suggested that concentrations of either gas above 10^{-11} Ci/l can be injurious over long exposures. They looked at experimental

(a) Attempts to extrapolate back to original exposure by measurement of the longer-lived daughters such as ^{210}Pb or ^{210}Po have been described in earlier chapters. Techniques for such measurements were not available when the first standards were developed for radon. The development of whole-body and in-vivo tissue counting have made this more feasible but still not easy.

work with small animals. They turned also to the lung cancer incidence among workers in the European mines discussed at length in chapter 3 and used the data summarized in table 3.2 of chapter 3 (which was table 3 in the Evans and Goodman paper). This gave radon concentrations in the various mines and in several parts of some mines. They then correlated the levels in the mines and in various shafts of the mines with cancer incidence in miners working therein to the extent possible.

Evans and Goodman used a broad brush to arrive at final figures. These were that long-continued breathing of air containing 10^{-9} Ci/l of either radon or thoron would result in a high incidence of lung cancer, and that exposures should be kept at less than one one-hundredth of this figure viz., 10^{-11} Ci/l or $10 \mu\text{Ci}$ (10 pCi)/l.

This figure was incorporated into the same NBS Handbook (NBS 1941) as the radium standard. It was intended to apply to work rooms rather than mines because there was no uranium miner enterprise in the United States in 1941. Nevertheless, as described in chapter 3, it was taken over later for the mines as well.

The historical record does not indicate whether or not the committee applied the same criterion as was used for radium in making its choice, viz., comfort with having one's own wife or daughter work in such an environment. However, it was the same committee, and presumably their chivalry extended from radium to radon.

There is no doubt that the level adopted was very conservative. Indeed, the permissible levels adopted for mining environments many years later and expressed in Working Levels (WL) (see chapter 3) are higher by a factor of at least ten.^(a) This fact has frequently gone unappreciated in the conversion to the WL system. Also, it represents one of the few instances in which a radiation protection guide developed in the early days was raised rather than lowered in later years.

Application of the WL concept detailed in chapter 3 has in effect drawn the focus of the standard for ^{222}Rn away from radon and placed it in the preformed daughters. This has introduced conceptual and computational steps not present in deriving the original standard or in the usual "industrial hygiene" approach. Fred Cross at Pacific Northwest Laboratory (PNL) (Cross 1979) has pointed out clearly, in a paper recommended to all who wish to delve further, that the WL-unit "ignores the 'form' of the potential alpha energy," e.g., how much comes from daughter products attached to ore dust, diesel smoke, and other vectors versus how much comes from unattached daughters, etc. As a result, as described by Morgan (cited in chapter 3), the radiation dose to the target tissue in rem does not bear a constant relation to WL or Working Level Months (WLM). This phenomenon was pointed out earlier by Morgan (1967) using the terminology of the MPC. He computed ratios of MPC to WL ranging from 0.11 to 170 depending on the properties of the inhaled aerosol. These are extremes, but they illustrate the point. Fortunately, the ratio is not far from unity for most typical mine conditions.

Thus, while it would be more logical, as Cross points out, to base the standards directly on the entities responsible for the biological effect, it seems likely that the WL-WLM concept will persist, possibly with more adjustment for the

(a) Because the Working Level is a much more complex entity, this comparison is very approximate but is basically true.

degree of unalterable R&A. New research and analysis can feed to this just as the earlier research fed to the original radon standard. It will be more sophisticated and not fully within the definition of a direct determination of standards, but close. The epidemiologic contributions remain "direct," of course.

Clearly the standards for radon, while hardly as inexorably derived from measurements of body or tissue burdens in humans and their correlated effects as in the case of radium, still rest largely upon a body of knowledge developed over long periods and involving effects in man. The enormous efforts detailed in chapter 3 have thus been put to much practical use.

C. Possible Interrelation of the Radium and Radon Standards

An interesting coalescence of the basis for the radium standard and that for radon was developed by Robley Evans on the occasion of extensive hearings on radiation exposure of uranium miners conducted by the Joint Committee on Atomic Energy of the U.S. Congress (U.S. Congress 1967). (By this time, the U.S. government knew there were serious health problems among the uranium miners on the Colorado plateau and convened the experts.) In response to a question on what scientific information existed that might contribute to determination of a proper standard for radon and its progeny, Dr. Evans introduced part of a document called CORD (Carcinogenicity of Radon Daughters). CORD contained the idea that carcinomas of the sinus epithelium seen in persons with appreciable radium burdens might be due to radon produced in situ. Evans presented many arguments concerning the basic similarities between the alpha-ray effects from radium in bone and those to sinus and bronchial epithelium from radon. He then presented data showing calculated doses to the sinus epithelium in a case that developed a carcinoma of the left frontal sinus (fifty-two years after radium injections) and measurements in another case that did not develop a carcinoma. These were direct measurements made on the 3.5-cm piece of frontal bone removed surgically with the carcinoma. The patient was cooperative to the point of allowing the surgical opening of the other uninvolved sinus for removal of an air sample. The MIT workers then measured the radon concentration in this air sample. It was thirty times that in the exhaled breath. Using this and information from other cases, Evans suggested that the effects of radon produced in vivo could be used by analogy for radon exposure to the lungs by inhalation (Evans 1967a). Thus, the idea of a direct approach continued in a different context.

There was some discussion that the two types of respiratory epithelium, lung and sinus, were not truly identical (Saccomanno at the same hearings, p. 659 et seq., also Parker p. 666) and about the fact that the radiation dose is partly from the radium in bone underlying the sinus epithelium. Furthermore, an entire appendix to the hearings was devoted to a critique of the CORD document, but further discussion here would get us into areas beyond our scope.

In 1969, an entirely new set of hearings was conducted on "Radiation Standards for Uranium Mining" (U.S. Congress 1969). This brought together nearly everyone from the scientific, administrative, labor, and industrial communities concerned and provides, along with the 1967 hearings, all anyone should ever need to know about what was being done about uranium miner standards and their relation to the radium standard. Although the mass of discussion makes extraction of basic philosophy difficult, it is obvious here too that epidemiologic evidence for effects and dose-response relationships were still at the heart of

any decisions regarding standards for exposure. Problems are in details of the statistics not the basic methodology. Even the most recent considerations by radiation protection organizations such as NCRP, discussed briefly in chapter 3, have the same base.

D. Standards for Natural Uranium

The derivation of standards for natural uranium has involved a mixture of the direct approach, as defined in this section, and the computational approach to be reviewed in section IV. To add complexity, there are two entirely separate endpoints in terms of effect. Because natural uranium is only weakly radioactive and is a moderately potent chemical toxicant to kidney, the process of standard setting has had to consider both chemical toxicity and radiation effects. In general, the direct approach has been applied more to chemical toxicity, while the indirect or computational approach has been applied more to the possibilities for radiation injury. We will emphasize here those circumstances in which the direct approach was used, but we cannot separate them entirely from the circumstances involving the indirect approach.

The basic saga has been told most skillfully by N. L. Spoor and J. B. Hursh in a chapter prepared for the monograph, *Uranium, Plutonium, Transplutonic Elements*, edited by Hodge, Stannard, and Hursh (Spoor and Hursh 1973).^(a) A companion chapter of equal stature in the same volume summarizes the experimental data on man (Hursh and Spoor 1973) and has been cited many times in earlier chapters. A somewhat shorter but crisp and useful summary was given by Hursh (1975) at the Conference on Occupational Health Experience with Uranium held at Arlington, Virginia, in April 1975 (ERDA 1975), under the auspices of the U.S. Energy Research and Development Administration (ERDA). Also, the saga was reviewed briefly by Stannard (1981) as part of a general paper at the Health Physics Society Twenty-Fifth Anniversary Symposium.

In contrast to the development of standards for radium and radon, the direct approach depended largely upon application of data from animals. The data on humans have been useful for validation of the standard, as we will see in section VIII. One reason for this difference is that occupational exposure to uranium in significant quantity had not occurred before the need to establish a standard became urgent.

The first standard was entirely empirical. Let us tell it in the words of Spoor and Hursh:

In 1944, before any experimental work had been completed there was an urgent need, in the Medical Section of the Manhattan Project, for a rough toxicological guide for the safety of those handling uranium in laboratories and plants. As production under war-time conditions had to proceed without delay some working rule had to be adopted immediately. They decided to adopt as the (MPC)_a [Maximum Permissible Concentration in Air] for uranium for occupational exposure the current (MPC)_a for lead, namely 150 $\mu\text{g}/\text{m}^3$. In the lead industry this limit had for a long time (since 1933, in fact) been regarded as an acceptable compromise between the demands of safety and those of engineering feasibility. In applying

(a) Hursh is, as we know, one of the key figures in internal emitter research, and we have seen his work in several chapters of this book. He worked at the University of Rochester. Spoor is a practical health physicist associated with the U.K. Atomic Energy Authority and had much opportunity to observe in-plant operations with uranium.

this figure to uranium there was no suggestion that lead and uranium were alike in their toxic effects or in the way they were handled by the body. It was chosen mainly because in the absence of any information to the contrary it was easy to assume that the toxicity of inhaled uranium, about which nothing was known, was comparable with that of lead, about which a great deal was known. As this air concentration had been attained in the lead industry, it seemed likely that it would be attainable in the uranium industry. This decision has been described by Hodge (1949) who pointed out that at this early stage the radioactive hazard from inhaled uranium seemed less important than the chemical toxicity. (Spoor and Hursh 1973, p. 244)

The primary site of the ideas was the Manhattan Project at the University of Rochester, but the decision involved the top management of the Medical Section of the Manhattan Project as well, e.g., Drs. Stafford Warren and Hymer Friedell (see previous chapters). The reference to Hodge (1949) in the above quotation is given in both chapters 2 and 9 (Voegtlin and Hodge).

As the large animal experiments at Rochester progressed (see chapter 9), it was obvious that soluble and insoluble compounds had to be dealt with separately. It appeared that chemical toxicity to the kidney would be the controlling injury for soluble compounds for the following reasons:

1. The amount of natural uranium deposited in lung, kidney, or bone would never constitute a radiological hazard. It was removed too rapidly.
2. The kidney injury is an extremely sensitive indicator of chemical toxicity, and an amount of soluble uranium in the atmosphere that fails to produce any kidney injury is a physiologically safe concentration. (Paraphrased from Spoor and Hursh 1973)

As detailed by Spoor and Hursh, the inhalation experiments at Rochester with dogs, rats, rabbits, and guinea pigs exposed for one year to air concentrations of soluble uranium varying from 40 to 2,000 $\mu\text{g U}/\text{m}^3$ were used to develop a recommendation. A safe level of 50 $\mu\text{g}/\text{m}^3$ was recommended tentatively as the (MPC)_a for soluble uranium. A useful summary of the data employed is given by Voegtlin and Hodge (1953, p. 1660) (cited in chapters 2 and 9).^(a)

To arrive at these summary figures, the very large effort detailed in chapter 9 was brought to bear. In the words again of Spoor and Hursh:

The Rochester experiments were conducted on a scale that is probably unequalled in the history of toxicology. The aim of the project was not in the first instance to provide one or two (MPC)_a values; it was rather to complete a comprehensive study, using different animal species, of the toxicology of several uranium compounds.

(a) It is a sad commentary on the lack of public understanding of the stresses of the war years and of the reasons for adopting a clearly empirical interim standard based on lead that over thirty years later this reduction from 150 $\mu\text{g}/\text{m}^3$ to 50 $\mu\text{g}/\text{m}^3$ was made the occasion by members of the Rochester press to castigate Dr. Hodge, who was the senior investigator, for having "overexposed" hundreds of MED workers. The reasoning was that all who had worked under the original higher level had been overexposed and should have been so informed. In view of the tightness of security in those days, it is hard to visualize how any such message could have been conveyed. Nor is there any reason to think a majority of the workers had actually been exposed to the original interim level, despite knowledge that some processes were performed relatively "dirty." Furthermore, the standards later went back up. Would the castigators be better satisfied if the scientists had not conscientiously reduced the level on the basis of the new information?

The task of marshalling and interpreting all of the data obtained presented a problem of considerable complexity. The results were published in detail, and the methods of interpretation explained in full. It is clear from the reports that no statistical methods were available, or conceivable, by which such a wide range of experimental data could be reduced to two (MPC)_a values. The authors explained that "decisions were hard to make in some instances because it was difficult to fit large masses of data that were occasionally perplexing or even conflicting into the four arbitrary classifications of (1) safe, (2) MAC, (3) borderline, and (4) toxic for the response levels."

(Spoor and Hursh 1973, p. 245)

Typical graphs embodying work on soluble uranium appear as figure 16.2A and B (taken from Voegtlin and Hodge 1953, p. 2207); there were numerous others for both soluble and insoluble compounds. This was the classic toxicologic approach. Nevertheless, the conclusions were regarded as tentative since there was full recognition of the possible differences between animals and humans.

A computational approach analogous to that used for radiation was applied to derivation of a standard for uranium in man. This was based upon an MPC of soluble natural uranium in kidney and the concept of a threshold chemical effect. As Spoor and Hursh explained, the value of 3 $\mu\text{g U/g}$ kidney was arrived at by a committee judgment based on the Rochester data.^(a)

The early approach to a standard for *insoluble* uranium was much less direct than that for soluble uranium. However, the early derivations were not woven into the computational system to be discussed in section IV and will therefore be taken up here. Basically it was decided that the long residence time of inhaled insoluble uranium in tissues, such as lung and pulmonary lymph nodes, greatly reduced the chance of chemical toxicity to kidney. It was concluded that here the potential radiation hazard would control. A calculation by William F. Bale at Rochester was made to determine the concentration of natural uranium that would deliver the then-accepted maximum permissible dose rate of 0.045 rem/day to the tissue. The result was 24 $\mu\text{g/g}$ of fresh tissue. Using the lung deposition figures from the one-year inhalation experiments with dogs and rats,^(b) it was calculated that exposure to 100 $\mu\text{g U/m}^3$ of air would result in a lung tissue content of 24 $\mu\text{g/g}$, the maximum allowable amount.

There were thus two limits, 50 $\mu\text{gm/m}^3$ for soluble uranium and 100 $\mu\text{g/m}^3$ for insoluble uranium.

It should be noted that neither this nor most later experiments with insoluble uranium produced evidence of radiation damage to the tissue. Indeed, as we saw in chapters 2 and 9, it took an eleven-year experiment of heroic proportions to finally produce, at levels far above the MPCs, clear-cut radiation damage from natural uranium. Thus, the criteria for soluble and insoluble uranium were basically different. The one involving chemical toxicity was derived from finding effects and assigning a threshold concentration. That involving radiation effects was based on an assumption regarding the permissible dose rate and a

(a) As we will see later, other data, such as half-time in the kidney, transfer functions, etc., were needed also and had to be gleaned largely from the animal data. Hursh (1975) takes the view that the application of the approach used for radiation to chemical effects was of questionable validity at best.

(b) Note that the lung deposition was determined from the experiments, not from a model as was done later.

FIGURE 16.2A. (Right) Graphical presentation of responses to UF_6 and UO_2F_2 exposures by inhalation. (Redrawn from Voegtlin and Hodge 1953, p. 2207.)

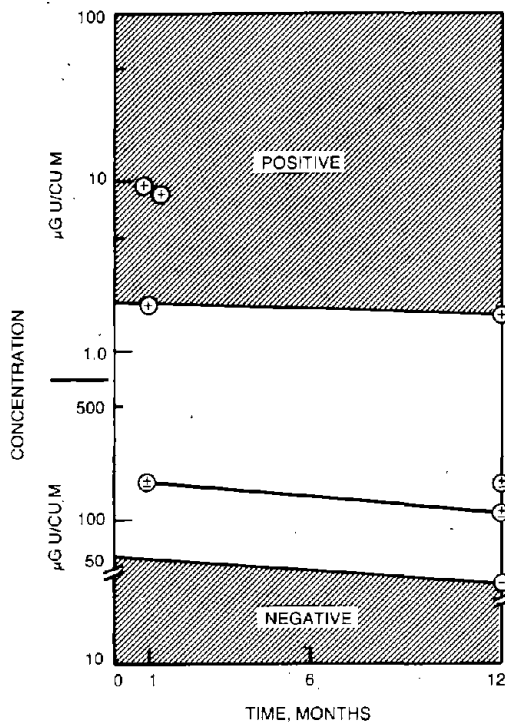
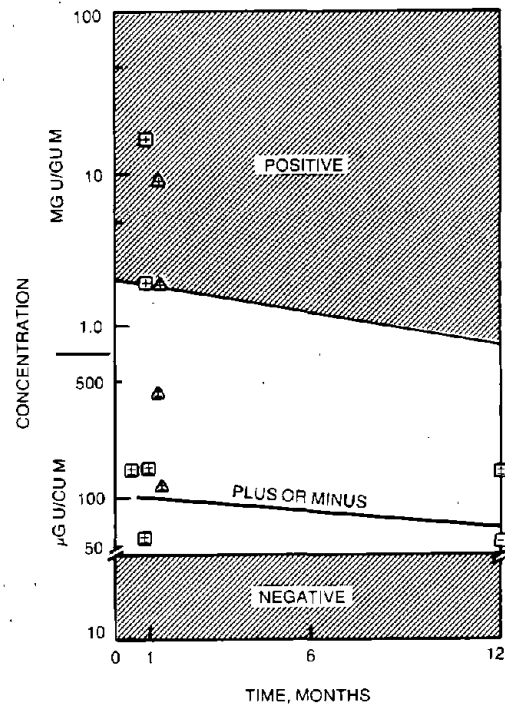


FIGURE 16.2B. (Left) Graphical presentation of responses to $\text{UO}_2(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ exposure by inhalation. (Redrawn from Voegtlin and Hodge 1953, p. 2220.)

calculation of the concentration expected to produce that dose rate in tissue using parameters developed from animal experiments. There followed a long series of revisions of both standards, all of them within an order of magnitude of each other, but ranging from $25 \mu\text{g}/\text{m}^3$ to $200 \mu\text{g}/\text{m}^3$. As Spoor and Hursh described, each revision was based on some new point of view or new data and ideas coming from the multitude of meetings and organizations we will review presently. The controlling process shuttled back and forth between chemical toxicity and radiation effects.

Probably the last of the direct determinations for uranium came from the American Council of Governmental Industrial Hygienists (ACGIH). They used the standard industrial hygiene approach of setting levels on the basis of experience in the work place. Whereas during the war some exposures to uranium were high enough to develop a considerable crop of cells and albumin in the urine of the workers, adherence to the recommended standards had appeared to bring these effects under reasonable control. In 1957, the ACGIH recommended limits of $50 \mu\text{g}/\text{m}^3$ for soluble uranium in air and $250 \mu\text{g}/\text{m}^3$ for insoluble uranium in air. These values were related explicitly to the Rochester experiments (Spoor and Hursh 1973) but included also some consideration of in-plant experiences (see, for example, several reports from industry at the 1975 ERDA Conference cited earlier, and also Hursh 1975). In 1968, the ACGIH changed their recommended limit to $200 \mu\text{gU}/\text{m}^3$ of air for *both* soluble and insoluble compounds of uranium. This was based on the fact that twenty-five years of industrial experience had failed to show "any definite association between exposure to higher levels of airborne uranium and injury either to the kidney or to the blood" (Spoor and Hursh 1973, p. 249).

This proposed increase raised some hackles in the radiation protection community, even before it was promulgated (Morgan to Stokinger 1967a; Stokinger to Schulte 1967, with copy to Morgan). Morgan's argument was that the measurement data were not very quantitative, and furthermore "some types of damage with which we are concerned may make their appearance long after exposure and the damage may be expressed in forms difficult to recognize, e.g., damaged kidneys that are more susceptible to certain diseases" (Morgan 1967a).^(a)

The members of the Threshold Limit Committee were nurtured in the conventional industrial hygiene approach (e.g., H. Stokinger, J. Quigley from National Lead, et al.), and the ACGIH figure has prevailed, except where limited by the U.S. Code of Federal Regulations, Title 10, on atomic energy.

Unfortunately, epidemiologic studies of uranium workers had been from crude to nonexistent. Only in the 1980s did useful analyses begin to appear. We will review these in section VII. Hence, there was little except metabolic data from humans to contribute further to the direct determination of uranium standards.

It may be noted that even today (1987) the choice of a proper basis for uranium standards, chemical toxicity or radiation effects, continues to shuttle back and forth. It is not a simple story.

(a) It is interesting to note that the levels derived by ICRP (see section IV) in 1958 corresponded to $210 \mu\text{g}/\text{m}^3$ for soluble uranium, based on chemical toxicity, and $180 \mu\text{g}/\text{m}^3$ for insoluble uranium, based on a limiting dose rate to lung of 15 rem per year. These levels were reiterated in 1962.

E. Standards for Plutonium

Standards were needed for plutonium, principally ^{238}Pu and ^{239}Pu , almost as soon as these elements appeared on the scene. Thus, the situation resembled that for uranium, only it was much worse. At least uranium had been around for many years and something was known about its potential biological effects (Hodge 1973). Plutonium was completely new. There was no backlog of experience to foster even a guess. Yet, as described in some detail in chapter 7, progression from microgram to kilogram quantities was to be accomplished over an incredibly short interval. Therefore, the only recourse for setting standards was initially by analogy, much as was done with uranium.

The story of how quickly we learned about plutonium is told in chapter 7. The concern for setting standards meant that almost every piece of new biological information was snapped up avidly for possible incorporation into a viable standard. During the days of World War II, the Metallurgical Laboratory, Los Alamos, Hanford, and Rochester were the centers for these activities. The early report literature, quoted in part in earlier chapters and in the book by Friedell (1983), traces the steps well. We are blessed with a superb summary of most of the important steps in a review prepared by Langham and Healy at Los Alamos (1973) for the same volume, *Uranium, Plutonium, Transplutonic Elements*, in which the Hursh and Spoor review on uranium appeared.

We will review here primarily the early stages of standard setting for plutonium since these relied largely on the direct approach. Most later developments involved a mixture of directly obtained toxicologic information and the calculation of radiation dose and will be saved for section IV.

Let it be emphasized that there was at the outset, and is to this day, no direct information on effects of plutonium in humans. Therefore, neither the direct observational approach applied to radium nor the industrial hygiene approach applied to radon and to some extent to uranium were available for plutonium. Instead, a series of inferences had to be made.

As soon as it was clear from the very early experiments of Joe Hamilton at Berkeley that plutonium deposited preferentially in bone, researchers sought to develop a standard for it based on ^{226}Ra . The first attempt was on the basis of the respective half-lives, i.e., 1,600 yr for radium versus 24,500 yr for ^{239}Pu . On this basis, it could be predicted that plutonium would be about 0.07 or one-fifteenth as toxic as radium. But this neglected the difference in energies. The average energy of the plutonium alpha particle is 5.15 MeV. The energy from ^{226}Ra is considerably higher, because of the energies of the several decay products. Assuming 50% retention of the radon produced in situ from the radium in humans (an old figure; it is now taken as 30%), the total energy from ^{226}Ra down to ^{210}Pb (radium-D, twenty-two year half-life), is about 14.4 MeV (alpha energy only). A more sophisticated calculation, and evidently one of the first (Langham and Healy 1973) was the following, based on the 0.1 μg limit for radium:

$$\begin{array}{ccccccc} \text{Maximum Permissible} & & \text{Maximum Permissible} & & \text{Ratio of} & & \text{Ratio of} \\ \text{Body Burden for} & = & \text{Radium Burden} & \times & \text{Half-lives} & \times & \text{Energies} \\ \text{Plutonium} & & & & \text{Pu/Ra} & & \text{Ra/Pu} \\ \text{or MPBB for Pu} = 0.1 \mu\text{g} & \times & \frac{24,500}{1,600} & \left[\frac{4.8}{5.15} + \frac{0.5(5.5)}{5.15} + \frac{0.5(6.0)}{5.15} + \frac{0.5(7.7)}{5.15} \right] \\ & & & & \text{}^{(226}\text{Ra)} & \text{}^{(222}\text{Rn)} & \text{}^{(218}\text{Po)} & \text{}^{(214}\text{Po)} \end{array}$$

$$\therefore \text{MPBB Pu} = 4.3 \mu\text{g} \approx 5 \mu\text{g}.$$

Before this standard could be promulgated, the autoradiographic evidence from the Berkeley group began to come in. It was apparent that plutonium deposited in bone quite differently from radium. As shown in figures 7.9, 7.10, and 7.11 of chapter 7, plutonium eschewed mineral bone and concentrated more in what was then called the "organic matrix." We can now pinpoint the localization as primarily on the endosteal surfaces of bone. Since these were already known to be intimately associated with bone growth, the early workers reasoned that alpha-particle irradiation might be more damaging in this area than if it were distributed largely in mineralized bone, as was ^{226}Ra . This raised a red flag regarding the relative toxicity of plutonium, even though it did not give quantitative information.

As a result of this, the first generally adopted standards within the MED appended some safety factors to the $5\text{ }\mu\text{g}$ possible level. The factor was taken as ten by the Hanford Operations people and five for the balance of the MED operations. The resulting maximum allowable body burdens were $1.0\text{ }\mu\text{g}$ ($0.06\text{ }\mu\text{Ci}$) for the MED generally and $0.5\text{ }\mu\text{g}$ ($0.03\text{ }\mu\text{Ci}$) for Hanford. These decisions were made primarily by Metallurgical Project people and at Hanford. As we saw in chapter 7, the discoverer of plutonium, Glenn Seaborg, was very active in assuring that adequate safety standards were instituted.

The first values for an air concentration level of plutonium were also derived by the direct method. As Langham and Healy (1973) described, S. K. Allison, director of the Metallurgical Laboratory in Chicago, wrote in March 1944 to J. R. Oppenheimer, director of Site Y (Los Alamos) that air containing $2 \times 10^{-15}\text{ g/cm}^3$ of plutonium ($1.2 \times 10^{-10}\text{ }\mu\text{Ci/cm}^3$) would be dangerous if exposure occurred for 48 hr/wk for two years. This was based on assuming that $50\text{ }\mu\text{g}$ of plutonium in the skeleton was equivalent in energy deposition to $1\text{ }\mu\text{g}$ of radium and that, since lungs weighed about one-tenth as much as skeleton, the equivalently dangerous level in the lungs would likewise be one-tenth of $50\text{ }\mu\text{g}$. Allison assumed a breathing rate of 10 l/min and evidently made no allowance for elimination from the lung. On this basis, the air concentration was:

$$\frac{5 \times 10^{-6}\text{ g}}{10^4\text{ cm}^3/\text{min} \times 2.8 \times 10^5\text{ min in 2 yr}} = \sim 2 \times 10^{-15}\text{ g/cm}^3$$

Note this was equated to $1\text{ }\mu\text{g}$ of radium, not $0.1\text{ }\mu\text{g}$ and thus was regarded as *dangerous*, not an allowable level.

Meanwhile, the animal experiments comparing plutonium, polonium and radium described in detail in chapters 7 and 8 were proceeding. We will continue the story by a quote from Stannard's review written in 1980 and published in 1981:

By 1947 the experimental programs began to bear fruit on all fronts. Contrary to the simple calculations it turned out that ^{239}Pu was more toxic than ^{226}Ra .

This was the beginning. By 1948-49 the Chicago work by Miriam Finkel, Austin Brues *et al.*, suggested a toxicity ratio of plutonium to radium of approx. 15 to 1. This would yield a permissible burden of 5/15 or $0.3\text{ }\mu\text{g}$. These figures went into the first TriPartite (U.S.A., U.K., Canada) Permissible Doses Conference in 1949 and a further reduction was made. The Conference adopted *protem* a maximum

plutonium body burden of $0.1 \mu\text{g}$ ($0.006 \mu\text{Ci}$). (a) This literal reaction to the toxicity ratio was clearly an over-reaction and the final version of the Conference report, done by the Canadians, lists $0.5 \mu\text{g}$ ($0.03 \mu\text{Ci}$). The literal reaction left out several important considerations. These were:

- The Chicago studies were based on injected dose. Pu retention in the rodent is 75% while radium retention is only 25%.
- The retention of radon differs between rodent and man. It is 15-20% in the rodent vs about 50% in man . . .

As described by Langham and Healy this situation led to an important meeting called in Washington in January 1950 by the late Dr. Shields Warren who was then Director of the new Division of Biology and Medicine of the Atomic Energy Commission. It is reported that Wright Langham gave a 2 hr presentation on the reasons the Chalk River values should not be adopted. He was followed by Austin Brues who presented the following, now classical relationship

$$1 \mu\text{Ci Ra} = \left[\frac{1}{15} \times \frac{0.75}{0.25} \frac{4.8 + 0.5 (5.5 + 6.0 + 7.7)}{4.8 + 0.15 (5.5 + 6.0 + 7.7)} \right]$$

The toxicity ratio in rodents	Retention ratio Pu/Ra in rodent	Energy ratios man/rodent- MeV modified by radon retention
--	--	---

$$= 0.4 \mu\text{Ci} (6 \mu\text{g}) \text{ Pu. (b)}$$

As Langham remarks, with perhaps too much modesty, it took Brues 5 min to make this presentation. If he had gone first the meeting could have been over in 10 min! My own view is that the numbers would probably have not fallen on such fertile soil if the need for a different view had not been emphasized by Langham. Besides, they could not have borne to come all the way to Washington and talk for only 10 min.

Dr. Warren is reported to have summarized the meeting with the suggestion that $0.5 \mu\text{g}$ ($0.03 \mu\text{Ci}$) could be viewed as equivalent to $0.1 \mu\text{g}$ ($0.1 \mu\text{Ci}$) of ^{226}Ra the

- (a) The reaction to this proposal at Los Alamos was violent. Langham, Harriet Hardy, who was there from MIT as a consultant, and others were certain that the laboratory could not possibly meet the stringent air concentration standards that a permissible body burden of $0.006 \mu\text{Ci}$ would entail. If this standard were adopted and enforced, the laboratory would have to shut down. In a very depressed mood, Wright Langham telephoned Robley Evans for advice and for help in finding a way out. He was convinced that the new level was wrong on biological grounds, not simply because it might shut down a major facility. To bolster Langham's morale, Evans suggested (Evans 1983) that he take a Filter Queen air sampler out into the woods of the mountains surrounding Los Alamos and compare the alpha activities there with those in the laboratory air. To Langham's delight, the readings from the pure, healthful, bracing mountain air were consistently and significantly higher than most of the laboratory air samples! There are, of course, some pitfalls in this because of the relative contributions of radon and its daughters in the two environments. But it served to revive Langham's spirits and give a holding argument while the complete story unfolded.
- (b) Note this is equivalent to $1 \mu\text{Ci}$ of radium. The "tolerance" value would, of course, be one tenth of this, or $0.04 \mu\text{Ci}$ ($0.6 \mu\text{g}$).

accepted maximum allowable body burden and that AEC operations could proceed on that basis.

In the ICRP-NCRP reports of 1954 and 1959 the figure is given as $0.04 \mu\text{Ci}$ which agrees with the derivation in the last equation with introduction of $0.1 \mu\text{Ci } ^{226}\text{Ra}$. (Stannard 1981 with slight modification and footnotes added)

The figure, $0.04 \mu\text{Ci}$ body burden of ^{239}Pu stood for many years. As described in chapter 8, the long-term experiments with beagles did not materially alter the picture. They confirmed and strengthened the validity of the toxicity ratios used. However, the system changed considerably from the direct to the computational approach. We will save further details, therefore, for that section.

An interesting variant of the direct approach to setting a standard for plutonium is found in calculations regarding a single intake. This might apply to a possible release from a fast reactor accident. The work was contained first in a Master of Science thesis prepared by H. G. Gavankar in the Department of Nuclear Engineering at the University of California, Berkeley under the general direction of Thomas Pigford and in collaboration with Patricia Durbin (Gavankar 1972). It was later presented at a topical meeting on Fast Breeder Reactor Safety held by the American Nuclear Society (ANS) in April 1974 (Gavankar, Durbin, and Pigford 1974). This came long after the computational approach had taken over. However, it utilized tumor risks estimated directly from the beagle dog experiments and related them to organ burdens. The abstract of the ANS paper tells the story:

This paper presents a method of assessing emergency radiation risks from a single inhalation of a $^{239}\text{PuO}_2$ aerosol. The ICRP Lung Model was used to calculate organ burdens and doses resulting from a single intake. Tumor risks have been estimated from experiments in which Beagle dogs inhaled $^{239}\text{PuO}_2$ particles (Thompson et al. 1972) or were injected with ^{239}Pu citrate (Mays et al. 1970); tumor risks could be related directly to organ burdens. We extrapolated lifetime tumor risks and expressed as (a) tumor risk/person/rem of organ dose accumulated over 50 years, and (b) tumor risk/person/nCi of organ burden (initial deposit in lung or 50-yr accumulated burden in bone and liver).

For purposes of illustration a "reference risk" was adopted—the published cancer mortality risk associated with the emergency dose guideline in existing reactor siting criteria (25 rem whole-body exposure in 2 hr). A comparison of tumor risks with the reference risk showed that 50-yr accumulated doses of 10 rem, 25 rem and 75 rem in the lung, liver and bone, respectively, were separately "risk-equivalent" to the reference risk. On a "total" risk basis (summation of independent incidences of tumors of lung, liver and bone from the same inhalation intake) the risk-equivalent intake varies with the particle size. For an ideal $0.5 \mu\text{m}$ AMAD aerosol, the risk-equivalent intake, about 19 nCi, results in 50-yr accumulated doses of about 7 rem, 8 rem, and 3 rem to the lung, liver and bone, respectively. Smaller particles pose greater total tumor risk; the risk-equivalent intakes of aerosols ranging from 0.05 to $3.0 \mu\text{m}$ AMAD were shown to be within the range, 9 to 36 nCi. (Abstract from Gavankar, Durbin, and Pigford 1974, references not reproduced.)

F. Other Radionuclides

We have now considered the principal instances where the direct approach to deriving a standard from effects data has been overtly and seriously applied. Somewhat less extensive and semidirect derivations can be cited for ^{224}Ra and ^{232}Th in Thorotrast.

1. Radium-224

In chapter 1, we reviewed the saga of the use of ^{224}Ra (ThX, half-life 3.64 days) as a therapeutic nostrum in German hospitals and a country doctor's practice over the period 1944 to 1951. Over two thousand patients were involved. Amounts given were ample to produce effects (40 to 5,000 μCi per person). However, the generation of effects required the usual long latent period. A standard was already in place by the time Spiess and Mays, at Utah and in Germany (see chapter 1), began their epidemiologic study. Thus, the information has been more valuable for validation than for setting of a standard. It may be useful in the future since ^{224}Ra deposits on bone surfaces initially, like plutonium, and, because of its short half-life, expends most of its alpha energy thereon. Thus it could, to a degree, be a useful surrogate for plutonium effects in humans.

Spiess and Mays (1973), and Mays and Spiess (1984) did derive figures from the effects data to quantitate the effectiveness of ^{224}Ra in juveniles and adults (see chapter 1). They used these to support the thesis that protraction of dose *increased* the effectiveness of alpha-particle radiation. This is, of course, the opposite of the usual effect of protraction seen with low linear energy transfer (LET) radiations. This phenomenon found its way into the third BEIR report (BEIR 1980, see especially pp. 411-414).

While no new or modified standards have resulted to date, it seems likely that these phenomena will be considered in future revisions of standards for short-lived radium isotopes.

2. Thorium-232 as Thorotrast

In chapter 4, we reviewed the accumulating biological data on the radiobiology of thorium isotopes. The largest exposed population of humans consists of patients who received a colloidal preparation of ^{232}Th with some added adjuvants as a radiocontrast medium called "Thorotrast." Here the problems are appearing largely as liver cancer. There is no doubt that the story has served to push the liver into a position of much greater prominence in consideration of radiation standards than was the case earlier. (Many other radionuclides, including alpha-emitting actinides, also deposit in liver to a considerable extent, as we have seen.) However, the dosimetry of Thorotrast is most difficult, and, until some current experiments are completed, the possibility of a chemically toxic component cannot be eliminated.^(a) Therefore, the data, although extensive, have not had much use to date for direct determination of standards. However, like the data for ^{222}Ra , they may play a part in the future, especially in establishing direct estimates of risks. An epidemiologic study of thorium dioxide in gas mantle manufacturing plants may also contribute in the future (Stehney et al. 1980; also Stannard 1983).

G. The Approach of the Federal Radiation Council

The plan and work of the FRC was taken up in section II. Its approach was enough like those described in this section to warrant identification here.

The work of the FRC began long after the computational approach had taken over for the general development of standards (section IV). Nevertheless, they

(a) These experiments at Utah have now reached the stage where chemical toxicity of the Thorotrast seems unlikely, but the first publications are not yet ready.

chose to analyze the pertinent information for important radionuclides on an individual basis. Their recommendations were thus idiosyncratic to a degree for each situation analyzed, although, unlike the very early direct approaches, they were done within a general framework of acceptable radiation doses and dose rates.

The radionuclides taken up by the FRC were primarily those in fallout from nuclear weapons testing considered first generically and then with specific consideration of ^{89}Sr , ^{90}Sr , and ^{137}Cs . There was also an in-depth review of the pathological effects of thyroid irradiation and thus, of course, the information on ^{131}I . Finally, the FRC worked in some depth on radon and its daughters, as discussed in chapter 3. Their operations were unique and original and their approach a mixture of the direct and the computational modes.

IV. The Computational Approach

A. Development

The process of nuclear fission added immeasurably to the number of radionuclides that needed consideration not only in terms of their behavior and effects (see chapters 6 and 7), but in terms of standard setting. Even during the war years, methods were worked out for calculating the radiation dose delivered to tissues by a variety of deposited radionuclides. These methods remained within the classified literature until the end of the war. The principles are clearly set forth in two early publications that are now to be regarded as classics and in one Metallurgical Laboratory report. The first publication, developed by Karl Z. Morgan and published in 1947 was based on a Met Lab report of 1945 (Morgan 1945), which was never published in full, although it was proposed for the National Nuclear Energy Series (NNES). It gave basic principles, general methods for calculation, and data for seventeen radioisotopes in different forms. This had obviously grown out of several years of work in the MED laboratories. The published paper was reproduced as a landmark paper in the Health Physics Society's Silver Anniversary volume (Morgan 1947 and 1980) and is thus easily available now.

A similar, but somewhat more generic report came from Waldo Cohn, who also worked in the Metallurgical Project at Clinton Laboratories (Cohn 1948). It too was reproduced in the cited Silver Anniversary volume as a landmark paper (Cohn 1980). It is not clear to what extent, if any, these two contributions represented interactions between the authors, nor is it important to establish this point. Both were at Clinton Laboratories for considerable periods, but Morgan began in the original Met Lab structure, even before the Clinton Laboratories were operational. Both used basic principles that had to underlie much of the MED biomedical consideration of radioactive materials.

The distinctive value of these is the development of a new and general approach. Obviously, there could be no retrospective analyses of experience in man for the hundreds of radionuclides that appeared *de novo* in nuclear fission. Even the data from animals had many gaps and, in terms of effects, concerned primarily relatively high doses (chapters 6 and 7). Generic analyses based on behavior of the stable elements helped. However, there was essentially no way to apply the direct approach described in section III. Yet, those concerned with standards wished to propose limits for all possible radionuclides as soon as possible. The answer was the development of a general system by which doses

could be calculated and related to an accepted "tolerance dose" or "maximum permissible dose." Secondary standards for intake or for concentrations in air or water could then be derived from these.^(a) Both the paper by Morgan and the one by Cohn are strong on use of first principles, which formed the basis for this system.

The Tri-Partite Conferences held in 1949, 1950, and 1953 (section II A.4) sparked the development of the computational system. By the completion of the third conference, the framework of an acceptable system for calculating standards had been developed, using the principles set out in the reports cited above, and earlier in the laboratories of the MED and also abroad. (The participants in these conferences are listed in section II.) Each individual and each laboratory contributed ideas and, once the plan had been agreed upon, each contributed important information concerning the behavior of individual radioisotopes in humans and animals.

The results of the three Tri-Partite Conferences fed in turn into the step-wise development of reports and tabulations by the internal emitter committees of the NCRP and ICRP (see section II).

There was first a statement from ICRP (1951) giving preliminary figures for maximum permissible levels and some of the data used for the most important radionuclides (^{226}Ra , ^{239}Pu , ^{89}Sr , and ^{90}Sr plus ^{90}Y , natural uranium, ^{210}Po , tritium, ^{14}C , ^{24}Na , ^{32}P , ^{60}Co , and ^{131}I). The report gave the background for each radionuclide.^(b)

Next came a compendium giving the normal behavior in the human body of all elements through $Z = 98$, plus data on limits for eighty-nine radioisotopes (ICRP 1955, NCRP 1953).

This major first phase culminated in comprehensive reports in 1959, which included approximately 215 radionuclides and 355 MPC values (ICRP 1959, NCRP 1959).

At this time, the committees of NCRP and of ICRP working on MPCs of radioisotopes were both chaired by Karl Morgan, and they worked closely together. Indeed, their reports appeared almost simultaneously. However, they were different. The ICRP's 1959 report gave details of the equations and methods of calculation along with tables of maximum permissible body burdens, critical organs, MPCs in air and water, and some of the biological input data. The NCRP's 1959 report, published as an NBS Handbook, gave all of the tables and some correlated information, but did not expand on the calculational methodology. Neither report gave full documentation of the origin of the input data.^(c) These were reserved for a special volume of the journal, *Health Physics*, which contains the report plus a bibliography for biological data, a bibliography for mathematical and physical data, and also indexes by authors and by elements, a monumental task (*Health Physics* 1960). While the reports are still quite generally available (they have been used for many years), this special volume of

(a) Some details of the mechanics of internal dose calculations are given in the chapter on Nuclear Medicine (chapter 20). The present discussion concentrates on the applications of the research data.

(b) Since this report was also published as a supplement to an NBS Handbook, we can be sure that both NCRP and ICRP participated, even though it is officially a report of the ICRP.

(c) The reports of the earlier fifties were rather completely documented. By the 1959 reports, the documentation was too extensive for a "handbook."

Health Physics is not so generally available. Yet, anyone wishing to trace in-depth the origin of any given figure in the ICRP/NCRP reports of 1959 must depend upon this source. It should be sequestered as a national treasure.

The members of the two committees that produced these invaluable compendia were:

National Committee on Radiation Protection and Measurements:^(a) Committee-2

K. Z. Morgan, Oak Ridge, Chairman
A. M. Brues, Argonne
P. W. Durbin, University of California, Berkeley
C. Failla, Columbia University
J. W. Healy, Hanford
J. B. Hursh, Rochester
L. D. Marinelli, Argonne
W. S. Snyder, University of Tennessee
S. Warren, Harvard (New England Deaconess Hospital)

For NBS Handbook 52 (NCRP Report 11) J. G. Hamilton, University of California, Berkeley; H. M. Parker, Hanford; and J. E. Rose, Chicago, also served.

International Commission on Radiological Protection:^(b) Committee II

K. Z. Morgan, U.S., Oak Ridge, Chairman
W. Binks, U.K.
A. M. Brues, U.S., Argonne
W. H. Langham, U.S., Los Alamos
L. D. Marinelli, U.S., Argonne
W. G. Marley, U.K.
M. K. Nakaidzumi, Japan
G. J. Neary, U.K.
M. N. Pobedinski, USSR
E. E. Pochin, U.K.
C. G. Stewart, Canada

Much of the detailed work for both NCRP and ICRP was carried out by the Internal Dosimetry Section of the Oak Ridge National Laboratory, e.g., Mary Jane Cook for collection and development of the biological data; Mary Rose Ford for physical data and computations; Janet Kohn and James Muir for effective energies and gastrointestinal tract values; all under the supervision of Dr. Walter S. Snyder.

B. The Basic System and Its Research Background^(c)

It is unnecessary here to describe mechanical details of the dose calculation approach adopted since they have been well documented in easily available sources and will be presented in chapter 20.^(d) We do need to set out briefly the basic assumptions made, the kind of data required, and the ways in which

(a) Now National Council on Radiation Protection and Measurements (section II).

(b) This represents the composition at the time the report was completed. In the period 1953 to 1956, A. J. Cipriani, Canada, served instead of C. G. Stewart.

(c) Since we are emphasizing history, we will concentrate on the system in operation for several decades and touch rather lightly on current practices. The uses of research data are not very different in the current system, only expanded.

(d) If the reader cannot wait for chapter 20, the excellent chapter by Snyder in the Morgan and Turner textbook is recommended (Snyder 1967 and 1973).

the research in the biomedical community reviewed in this book has contributed to it. We need also to review some of the research done specifically for the system.

Originally the system was applied primarily to occupational exposure. The following plan was adopted:

1. Intake occurred either continuously for a full 168-hr week or continuously over a 40-hr work-week.
2. Intake limits were devised so that the dose rate in a critical organ or the whole body would never exceed the stated maximum permissible dose rate during a working lifetime, assumed to be fifty years.^(a) Except for those radionuclides that deposit in bone, the maximum permissible dose rate was based on experience with external radiation sources.
3. A quantity known as the "effective absorbed energy," which considered both the physical properties of the isotope (see chapter 20) and the relative biological effectiveness, later called the "Quality Factor," of the radiation type emitted by each radionuclide, was calculated for each organ and the body as a whole.
4. Information on the distribution of each radionuclide to body tissues was assembled. The accumulation of dose to each organ or tissue and the associated maximum permissible body content was calculated from this information. Of these, the organ or tissue resulting in the most restrictive air and water concentrations and the lowest permissible body burden was usually selected as the "critical organ." Only when this selection process pinpointed a tissue of obvious radioresistance or an organ of little biological significance and there were other tissues with nearly the same concentrations would the "critical organ" be other than the one with the highest concentration of radionuclide. With isotopes of more or less uniform distribution, the whole body became the critical organ. In many instances with poorly absorbed substances the gastrointestinal tract might be critical, at least under the conditions of more or less constant intake.
5. The tabulations usually showed the maximum permissible body burden and derived figures for a number of organs. The more restrictive ones were placed in bold type. Behind the scenes, many other organs were also calculated, indeed, nearly all except for radionuclides with very specific localization. However, many were not shown in the tables since they were beyond any possibility of being critical.
6. Derived limits (the real operational limits called maximum permissible concentrations) were calculated for radionuclides in air (MPC_a) and water (MPC_w) for intake over a normal work week and also for continuous intake. To derive these, many assumptions had to be made. These included the normal fluid intake by workers, the behavior of various segments of the gastrointestinal tract in terms of times, masses, etc., and the behavior of inhaled materials. These necessitated the development of many general biological models (see section VI) as well as the data for specific isotopes.

What did the internal emitter research data contribute to this operation? A great deal, as shown below:

1. The storehouse of information on tissue distribution of radionuclides was used to calculate organ doses and to derive the critical organ. At the time the

(a) In some of the earlier calculations, the dose to seventy years was used.

effort started, the information we have summarized in chapters 6 and 7 was the primary source. This was a good start, but led to the following statement in the introduction to the ICRP's 1955 report:

Ideally, one would prefer to select maximum permissible body burdens and maximum permissible concentration values that are based on observations on humans who have consumed the particular radioactive material under the conditions and over a period of time approximating those set forth as being applicable to the maximum permissible values selected. Only in the case of radium, however, does one have an accumulation of human experience over a period of years that is suitable to serve as a basis of selection of these values. In a few cases the chemical behavior of other elements is sufficiently similar to that of radium so that comparisons with radium may serve as a basis of choice of maximum permissible values. Usually, however, human data are lacking completely for a particular radioisotope and in such cases data from limited animal experiments must be extrapolated to man. Sometimes even animal data are not available and in such cases estimates are made from a comparison with elements having similar chemical properties and/or from an investigation of the body retention, distribution and elimination of stable isotopes of the radio-element under consideration.

(ICRP 1955, p. 23)

Every new experimental finding of the ensuing years (chapters 8, 9, and 10) got plugged into the system avidly.

2. Information was needed on the retention kinetics of each radionuclide, i.e., not only where did it go, but how long did it stay, and what was the time course of its release? The results of the internal emitter research were used for calculation of the biological and effective half-lives (see chapter 20) for each radionuclide.
3. Numbers were needed for various transfer functions such as:
 - a. fraction of radionuclide passing from gastrointestinal tract to blood;
 - b. fraction passing from blood to critical body organ;
 - c. fraction in critical organ to that in the total body;
 - d. fraction of that taken into the body that is retained in the critical organ.

Each of these received a symbol in the formulations and was derived as best possible from the research data. The steady flow of new work (chapter 8) contributed enormously to the ongoing effort. Yet, a majority of the references in volume 3 of *Health Physics* (1960), where the references for ICRP Publication 2 were brought together, are not much later than the middle 1950s, and many go back to the 1930s, particularly those concerning the behavior of the stable isotopes of certain elements.

C. Bone Seekers

An entirely different approach was used in the first computational approach for those radionuclides that deposited primarily in bone. The reliability of the standard derived for ^{226}Ra (section III) was fully recognized. Instead of applying the maximum permissible dose rate used for other substances, the system for the bone seekers used the permissible body burden of ^{226}Ra as a bench mark (i.e., $0.1\ \mu\text{Ci}$ or μgm). Other bone seekers were related to it by a comparison of the energy deposited in bone by the particular radionuclide as compared to that deposited by $0.1\ \mu\text{Ci}$ of ^{226}Ra and a fraction of its daughter products. The relationship used is shown in note 1 at the end of this chapter.

To accommodate the greater effectiveness of those bone seekers that deposited on bone surfaces, a factor, n , was introduced into the formula for effective energy.^(a) This factor n (originally written as the Greek letter, “eta,” but soon called the n factor) was taken numerically to equal one if the parent element of the chain was an isotope of radium or if the original energy component was x-or gamma-radiation. It was taken as five in all other cases. It was called the “relative damage factor” in 1959. Because the difference in damage between these radionuclides was thought to be resident in the details of their distribution pattern within bone, discussed many times in this book, it was sometimes known also as the “distribution factor.”

This system obviously wove in some of the features of the empirical toxicity ratio discussed in connection with plutonium in section III E. However, it was still a computational approach. It allowed for only two relative toxicity ratios, one or five. The reason NCRP/ICRP did not use toxicity ratios directly and to the full is addressed in ICRP 1959: “When the necessary data are available, the maximum permissible body burden, q , of a radionuclide may be determined by a comparative study of the clinical findings and biological damage produced by various quantities of ^{226}Ra and the radionuclide under study. Studies of chronic exposure—a few of which have been started—should furnish the most direct and reliable values of q . Until these studies have been completed it may be necessary to continue to determine values of q by a direct comparison of the energy deposited in bone. . .” (ICRP 1959, p. 13, reference in text omitted).

What was not said was that the toxicity ratios available then involved only experiments on short-lived rodents, and there was concern that they might not apply to humans. They were, as we saw in chapters 7 and 8, truly chronic experiments for rodents, but they did not cover the time span desired for a truly “chronic” experiment. This needed longer-lived animals or humans.

We saw in chapter 8 that the toxicity ratios from the large experiments with beagle dogs turned out to be fully consonant with any values that might have been derived earlier from the experiments with rodents. Nevertheless, the system was never altered. The somewhat confusing and painfully limited n factor continued in use until the new systems for bone based on calculation of dose to the endosteal layer of cells in bone (see chapter 20, also ICRP 1979 and NCRP 1985a)^(b) took over. The beautiful confirmation of the rodent data was recognized but never really pushed the system in the direction indicated in the 1959 ICRP discussion quoted above.

Perhaps one reason for this is the fact that clinical data on humans under chronic exposure conditions had accumulated only for ^{226}Ra , ^{222}Ra and their daughters, and ^{224}Ra . By the original definitions, n would be one for all of these.

(a) Effective energy was then defined as $\sum E F (\text{RBE}) n$ where the E , F , and RBE factors are as defined in note 1. RBE later became Q , the Quality Factor.

(b) This is only one of many major changes introduced by ICRP Report No. 30 and the commentary by NCRP. The approach depicted in figure 16.3 was replaced by the concept of committed dose (see chapter 12). Critical organ was dropped, and the terminology was changed in less major areas. Much of this was alluded to earlier. Since the uses made of research data were not significantly different, we will not repeat the new formulations here. The net effect has been the need for still more research data because of the increase in the number of isotopes considered and the number of parameters for each isotope. The interested reader should consult ICRP 1979 and NCRP 1985a.

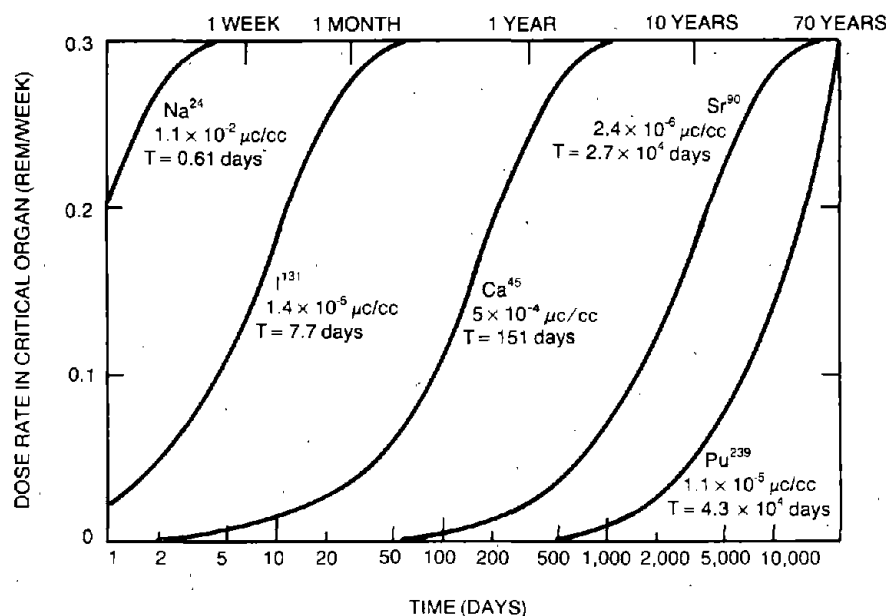


FIGURE 16.3. The increase in dose-rate to the critical body organ as a result of continuous use of water contaminated with indicated radioisotopes of different effective half-lives is shown. The concentrations used in making these plots are given to the right of each curve and differ somewhat from the maximum permissible values in the report, where other factors influenced the actual choice of maximum permissible concentrations. (Redrawn from ICRP 1955, p. 33. Reprinted with permission of *The British Journal of Radiology*, London, England, copyright 1955.)

We know it should not be one for ^{224}Ra , since ^{224}Ra behaves more like plutonium than it does ^{226}Ra . Another exception would be thorium, and we have already discussed the problems with it.

There are other complexities beyond our scope here. Suffice it to point out that the NCRP/ICRP maximum permissible body burden for ^{239}Pu using the above computational approach came out to be $0.04 \mu\text{Ci}$ using bone as critical organ, essentially identical to that calculated by the direct method as shown in section III. This was more than a coincidence! We can see how the n factor got its value of five for isotopes other than radium.

The failure of direct utilization of the empirical toxicity data for modern standard setting has been a disappointment to some of the most involved investigators. This was what started the king-sized experiments originally (chapter 8)! However, since the new information indicated nothing was seriously wrong with the figures derived by the computational method, and thoughts were going in other directions, we cannot be unduly distressed that the system was not accommodating. The research data made large contributions to our knowledge of the behavior of bone-seeking radionuclides and their effects despite this possible hiatus. Also, they were used behind the scenes as a control or to "fine-tune" some of the results of dose computations.

D. Special Features of the Basic System and Some Modifications

1. Special Features

It must be emphasized that this basic system had some unique features. In the case of short-lived radionuclides or any that were rapidly eliminated from the body, the limiting dose rate might be reached within a few days or weeks. From that point on, it was assumed that equilibrium existed between intake and loss. The equations used are shown in note 2 at the end of this chapter. In the unlikely case of actual continuous intake as postulated, the critical organ would thus receive the limiting dose rate from that time onward. By contrast, elements with long half-lives and prolonged retention would approach the limiting dose rate very slowly. Indeed, the maximum permissible organ burden associated with the limiting dose rate might be reached only at the end of the assumed lifetime of occupational exposure. These phenomena are illustrated in figure 16.3, taken from an early ICRP report.^(a)

Obviously, this system involves a considerable factor of conservatism for the long-lived, long-retained radionuclides, especially since intakes are most unlikely to be continuously at the MPC.

It should be noted that no cognizance is given in the system to the nature of the biological effect being protected against. The limiting dose rate was determined by groups espousing basic radiation protection criteria. They arrived at their conclusions largely on the basis of work with external radiation sources, except for the bone seekers. They applied their best judgment to the biological data and set exposure levels for the most sensitive functions. For this reason, when the critical organ was whole body, lens of the eye, gonad, or red bone marrow, the allowable dose differed from that for the average tissue.

Genetic effects were included in the consideration, although, as we will see presently, very little information had been gathered at that time on the genetic effects of deposited radionuclides.

As a result of this lack of specification of the effect being protected against, it was the metabolic data on radioisotopes, i.e., distribution, excretion, transfer function, etc., that contributed most. Except for the bone seekers, the accumulating data on effects were not used. Only later did they make a fuller contribution to standard setting.

The chemical form of the isotope was considered, but not nearly to the extent the internal emitter research might have supported. We have seen throughout this book and the cited literature that there are many chemical forms of many radionuclides, and the form sometimes can have a profound influence on biological behavior. However, the committees had to simplify. They simply sorted compounds into two categories, "soluble" and "insoluble," and utilized data for the compounds that best fit the description and were important.^(b) Fortunately, the early researchers had faced this same dilemma and, as we saw with uranium in section III, had also used only the two broad categories, "soluble" and "insoluble." The distinction was applied primarily to inhalation exposures, but not always. Later work developed a more sophisticated system that

(a) At this time, the period of exposure was taken as seventy years, but the principle is the same. This early illustration was chosen to show that this feature of the system was recognized from the beginning.

(b) This applies to the 1959 system and derivatives from it, not to current practices.

utilized more completely the accumulated fund of research data on the influence of chemical form.

All of these special features were fully recognized by the investigators and decision makers as necessary simplifications to allow development of a workable system in a finite time. Some have been eliminated or modified by more advanced systems. Nevertheless, these and other features that will be apparent when we discuss models should be recognized.

2. Modifications

a. Single Exposures

No mechanism was given in the basic system for determining the limits for, or the consequences of, a single intake or a brief series of intakes, except to note that anything less than a continuous intake brought in a factor of conservatism.

Karl Morgan (with Walter Snyder and Mary Ford) took up the question of MPCs of radioisotopes in air and water for short-period exposure at the first Atoms for Peace Conference in Geneva, Switzerland (Morgan, Snyder, and Ford 1956).^(a) The problem at hand can best be stated by quoting from the paper:

Although continuous exposure (MPC) values are necessary for all work with radioactive material, they do not answer many questions relative to the hazards associated with the occasional accident or spill of a radioactive material, and the resultant exposure of short duration—usually referred to as a *single exposure*. . .
(Morgan, Snyder, and Ford 1956)

The same basic types of biological and physical data were needed and employed as for continuous exposure, but the permissible dose was put in three time frames: one week, one year, and seventy years. Also, a detailed appendix was given for derivation of the dose resulting from single exposures to radioisotopes. Any modifications of the biological half-life or other functions attendant upon the single-exposure mode were incorporated into the calculations.

Morgan et al. developed tables showing a function called the "MPI," which was the μCi present initially in the volume of air to be breathed during the succeeding eight hours that resulted in the indicated dose (weekly, yearly, or lifetime limit) for inhalation exposures. It was applied also to injection and puncture wounds. The critical organ after intake might become any one of the tissues important to the basic system. To simplify matters, they chose five situations and developed MPIs and relative hazards for eighty-one radionuclides as follows:

- Case 1—*inhalation of soluble material—critical body organ may be total body, muscle, fat, bone, blood, skin, liver, kidneys, spleen, or thyroid*
- Case 2—*injection of a soluble material by a puncture wound*
- Case 3—*injection of an insoluble material by a puncture wound*
- Case 4—*inhalation of an insoluble material with the lung as critical organ*

(a) It is unclear whether or not this effort received any input from the NCRP/ICRP internal dose committees or was a solo performance by the Oak Ridge group. This author is inclined to believe it was the latter, since the later "official" reports, to be discussed presently, went in another direction.

Case 5—inhale of an insoluble material where some portion of the gastrointestinal tract is the critical body tissue.

The tables are extensive and go through from one to several isotopes of elements up to $Z = 96$ giving either MPI or μCi injected that will result in the allowable weekly (0.3 rem), yearly (15.7 rem), or lifetime dose (150 rem in seventy years). They also give the weight in milligrams corresponding to the smallest value of the above and a calculation of the relative hazard of the radionuclide.

The authors point out that "no official MPI values for single exposures have been agreed upon . . ." and present the figures with the hope they would be useful in "making the final selection of the MPI values for single exposures." Evidently no such action was ever taken. The ICRP reports (see below) on the subject use the same limiting doses as for continuous exposure. They evidently preferred the concept of dose commitment.^(a) Nevertheless, this compendium by Morgan and colleagues was carefully thought out and used the biomedical data effectively. It is surprising that it has not been used more or quoted more, especially since it stood alone for many years.

Over a decade later, the ICRP addressed single intakes in its Publication 10 (ICRP 1968). Here the radiation dose was calculated as a time integral expressed in μCi -days resulting from deposition of 1 μCi . With suitable constants to convert to absorbed radiation dose, the legacy of a single intake could be developed. For occupational exposures, the period for integration was chosen as fifty years. Out of this came the concepts of committed dose, "S" factors, etc., which are taken up in chapter 20.

In both this and the earlier work by Morgan, the application of the metabolic data from experiments where only a single dose was given, which was true of much of the animal work, was probably somewhat more germane than it was to the basic system. We have no evidence of real problems resulting from this dichotomy, but it must be recognized as a flaw in the available research data.^(b)

A few years later, the same committee (Committee-4) of ICRP addressed the kinetics of several intakes in a limited period as well as translocation of radionuclides from an organ of initial deposition (e.g., lung or wound) to other organs (ICRP 1971). This was more a variation of computational methods than the entry of new research data, except for those on translocation and elimination.

These reports contained references to many of the new documents used and went back by use of appendices to the practice of presenting data on individual radionuclides. They also tabulated the metabolic information used.

Finally, these reports introduced the concepts of investigation levels and derived investigation levels.

The members of ICRP Committee-4, a committee that had fairly broad charges, were:

- (a) A review of the entire development given by Morgan in 1971 at an International Atomic Energy Agency (IAEA) symposium indicates that this was indeed the case and gives the reasons (Morgan 1972).
- (b) A very current NCRP report (NCRP 1985a) contains a theoretical mathematical analysis of the long-term differences in tissue content of radionuclides received as single or an annual dose and shows that the difference is small in the long term. This may or may not apply across the board, but it simplifies prospective standard setting.

H. Jammet (Chairman, France)	D. Mechali (France)
D. J. Beninson (Argentina)	C. Polvani (Italy)
G. C. Butler (Canada)	R. Recht (Belgium)
H. T. Daw (U.A.R.)	E. G. Struxness (U.S., Oak Ridge)
H. J. Dunster (U.K.)	F. Western (U.S., AEC)
K. Koren (Norway)	B. Windeger (U.K.)

A task group consisting of Butler (Chairman), Daw, Polvani, and Stewart, plus G. W. Dolphin (U.K.), J. Lafuma (France), W. S. Snyder (U.S., Oak Ridge) and J. Vennart (U.K.) prepared the reports, with help from S. R. Bernard (U.S., Oak Ridge), I. S. Eve (U.K.), M. R. Ford (U.S., Oak Ridge), P. E. Morrow (U.S., Rochester), G. P. Howells (U.K.), and S. D. Simpson (Canada).

b. Population Exposures

The "system" as described was developed for occupational exposures. The problems of radioactive fallout from nuclear weapons tests (chapters 12 and 13), siting of nuclear power plants, and the general arousal of interest in environmental contamination pushed the standard setters into making judgments on allowable population exposures. We saw some of the environmental aspects in chapter 15. The basic story is told well in the various reviews of radiation protection philosophy. The possibility of genetic damage played a large role in the early decisions. However, this was primarily based on work done with external radiation. Only the most rudimentary experiments were done on the genetic effects of internal emitters. They were no help in establishing population exposure levels in the 1960s. The only recourse was calculation of the dose to gonad. Fortunately, few radionuclides concentrate specifically in either ovary or testis. The dose to gonad was frequently larger from radioisotopes deposited in surrounding tissues such as bone than from the deposition in gonadal tissue.

Of the hundreds of radioisotopes listed in the tables, only four (tellurium, tin, zinc, and chromium) turned out to have a portion of the reproductive system^(a) as potentially critical. Only one was close enough to being the critical organ to be placed in bold type.

The limiting levels for external radiation for populations were developed simply by use of a scaling factor, usually one-tenth, from the occupational levels. The same was done for radionuclides, with a few exceptions. Most especially the all-important U.S. Code of Federal Regulations Part 20 and related parts simply gave two tables with the figures for population exposure a factor of thirty lower than those for occupational exposure.^(b)

Our review of the metabolism of radionuclides at environmental levels seen in chapters 13 and 15 gives many reasons to believe that the various metabolic constants derived from higher levels may not always apply to these very low levels. Despite the now large accumulation of information on radionuclides at environmental concentrations, it cannot be said that the basic system has been redone for population exposures with the insertion of metabolic values pertinent to the environmental situation.^(c)

(a) This included the prostate gland.

(b) There were a few specific exceptions based on field findings, e.g., iodine from water-cooled reactors, as we saw in chapter 15.

(c) Morgan and colleagues called attention to the potential for such developments as early as 1959 at the second Atoms for Peace Conference in Geneva, Switzerland (Morgan, Tipton, and Cook 1959).

In recent years, actual experimental work has been done to test for genetic effects of deposited radionuclides. The work has been summarized by the Task Group on Genetic Risk from Internal Emitters of the NCRP Committee on Internal Emitter Standards (NCRP 1985b). It appears that, while there are some special situations, in general, the genetic risk from radiation doses and effects produced by deposited radionuclides are not likely to be greatly different from those from externally applied doses. Thus, the biomedical information on genetic effects does not dictate any urgent need for population standards for radionuclides separate from those derived from experience with external dose effects. On the other hand, the differences in metabolism at environmental levels may dictate special consideration for some radioisotopes. This is a significant gap.

E. Concentrations of Stable Elements

Many of the radioisotopes of interest in the early development of the computational scheme were isotopes of elements normally at very low concentrations in the human body. As the enterprise gained momentum, it was obvious that there was not sufficient information on either the radioactive or stable isotopes of many elements to determine metabolic behavior, select critical organs, etc. Also, knowledge of the concentrations of the stable isotopes of these elements in humans was needed for the development of "Reference Man" (section VI C), determination of pool sizes, etc.

This led to the development at the University of Tennessee in Knoxville and at Oak Ridge of a significant research enterprise to make the necessary determinations, one of the few in-house experimental programs developed specifically around the problems of internal dosimetry.

Dr. Isabel Tipton, an experienced spectrographer and physicist at the University of Tennessee was persuaded to embark on a program with trace metals. It developed into essentially a career with numerous publications appearing year by year with and without collaborators.

The protocol was to use fresh autopsy material from accident victims. Of course, Dr. Tipton never knew how plentiful or how scarce her basic materials might be. However, in view of the tediousness of quantitative spectrographic work, particularly in the earlier days, we can imagine her job was a continuous one. The data were applied directly to the calculations of the Oak Ridge internal dosimetry group.

The information developed in this enterprise contributed also to the growing interest throughout the world in the biology and biochemistry of trace elements in humans and animals. Thus, we find Dr. Tipton appearing on programs with people like Dr. Henry Schroeder, who made at least one career out of the biomedical significance of trace elements.

Since the work of Tipton and her colleagues is scattered over time and in many places, and since her husband, Dr. Samuel Tipton, supplied this author with a nearly complete set of papers, a full bibliography of this important work is given as note 3 at the end of this chapter. This is done to recognize Tipton's role in the internal emitter research effort.

The group at Lawrence Livermore Laboratory (LLL) got together a computer-coded compilation of published information on elemental concentrations in human organs in both normal and diseased states (Anspaugh et al. 1971). This appeared as a UCRL report in three parts. The first part gives the raw data by

atomic number, subordered by organ and suborgan. Also listed are method of analysis, geographical source, age, sex, and number of individuals. In the second part, the data are ordered by atomic number and subordered by organ, suborgan, and general health state. The third part orders the data by organ and suborgan; suborders them by atomic number and general health state. The number of studies, number of individuals, range of high and low means and of individual values, etc., are also given. The second and third parts are more summary in nature than the first.

This very important compilation contains a bibliography of two hundred references in the first volume. It is not easy, however, to ferret out the specific literature reference(s) pertaining to the origin of the data in the second and third parts.

V. Metabolic Data and Metabolic Models^(a)

The importance of the information on the behavior of each radionuclide in the body to the process of standard setting is obvious from the earlier parts of this chapter. Our intent here is to discuss, largely in broad terms, some of the characteristics of the data and the general models that have been developed. This enterprise has drawn extensively on the knowledge gained in conventional pharmacology, physiology, and toxicology, as well as from radioisotope research. However, we will conserve space by concentrating on work concerned primarily with radionuclides.

Each chapter has contained partial reviews of the development of pharmacokinetic data for the nuclides of concern therein. The reader is urged to review these for specifics applicable to this section.

A. Retention Kinetics

Throughout this book, expressions for the retention of radionuclides in organs and tissues have been alluded to. In most instances, two or a series of exponential functions of time described the data reasonably well. For the 1959 NCRP/ICRP reports, the simplifying assumption was made that the loss rate from any tissue could be represented by a *single* exponential function.

Usually, the constant for the longest biological half-life in a multiple exponential series was adopted. Thus, a long biological half-life was utilized, even when a large portion of the material might actually be eliminated by a rapid initial process. This simplification was needed to develop the system. Clearly, it applied a factor of conservatism of varying magnitude to nearly every MPC calculation.

By the time of ICRP Publication 10 and subsequent work, more complete expressions for retention were given. The current system, developed for ICRP Publication 30 (ICRP 1979), gives the complete expressions for retention with full references.

Nevertheless, the system developed in the 1959 NCRP/ICRP reports was used for nearly two decades. The results of utilizing the single exponential scheme thus had many years for impact. Were there problems?

(a) We are using the term "metabolic" in a somewhat colloquial sense, in line with common usage in the radioisotope field and in general toxicology. We mean the behavior of the entity in the body in terms of distribution, excretion, retention, etc. A more eloquent term would be pharmacokinetics.

In chapter 1, the appropriateness of a power function for describing long-term retention of radium (largely ^{226}Ra) in long-lived animals and humans was emphasized. Also, the contrasts between these species and rodents were set out. There was evidence that other long-lived, long-retained bone seekers followed a similar pattern. The 1959 ICRP report devoted a special section to consideration of the power function as one alternative to the single exponential in determining MPCs for bone seekers. Calculations and a table in ICRP 2 give MPC values derived by a power function model for isotopes of strontium, radium, uranium, and plutonium. This was expanded on by Morgan, Tipton, and Cook (1959). The comparison is shown in table 16.1.

TABLE 16.1. Examples of $(\text{MPC})_w$ and $(\text{MPC})_a$ Values Calculated* by the Exponential Law and by the Power Law

Radionuclide	Critical organ	q (μC)	Values Based on Exponential Law		Values Based on Power Law	
			$(\text{MPC})_w$ ($\mu\text{C}/\text{cc}$)	$(\text{MPC})_a$ ($\mu\text{C}/\text{cc}$)	$(\text{MPC})_w$ ($\mu\text{C}/\text{cc}$)	$(\text{MPC})_a$ ($\mu\text{C}/\text{cc}$)
$^{90}\text{Sr} + ^{90}\text{Y}$	Bone	2.1	5.4×10^{-7}	4.4×10^{-11}	8.3×10^{-6}	6.9×10^{-10}
$^{226}\text{Ra} + 30\% \text{ drs.}$	Bone	0.1†	1.2×10^{-7}	9.8×10^{-12}	1.2×10^{-6}	1.0×10^{-10}
^{238}U -natural	Kidney (chem. toxicity)	4.7×10^{-3}	2.9×10^{-4}	1.3×10^{-11}	8.4×10^{-4}	3.7×10^{-11}
^{239}Pu	Bone	0.044	4.5×10^{-5}	5.9×10^{-13}	4.0×10^{-5}	5.3×10^{-13}

* Values in this table are "calculated" values given only for comparison of the exponential and the power law and are not necessarily the final q and MPC values recommended by the ICRP.

† National Bureau of Standards, Handbook H27, Safe Handling of Radioactive Luminous Compound, (1941) Superintendent of Documents, Washington 25, D.C.

Source: Reset from Morgan, Tipton, and Cook 1959. Reprinted with permission of Pergamon Press, Elmsford, New York, copyright 1959. For definitions of q , MPC, etc., see notes 1 and 2.

All values derived by use of the power function are significantly higher than those derived by the exponential method. This was explained, as stated above, by the conservatism of using the longest biological half-life and a rather large value for the fraction of material in the blood that has the long half-life. The MPC values derived from power function retention kinetics were never recommended for use.

This was not a crass disregard of the biomedical data. Let the report state the reasons:

While the MPC values listed in the accompanying table were considered by the Committee in making their final decision, they are not to be considered as recommended values. They are listed to indicate that the Committee has considered carefully this method of estimation and to stimulate research concerning the interpretation and validity of this model. The presentation of the biological data in table 12 on the basis of the exponential model is in large part dictated by the desire to give a unified and economical presentation of the material.
(ICRP 1959, pp. 38-39)

Thus, while the power function fitted the data very well, as we have seen in earlier chapters, the simpler and more conservative choice for protection was the dominant consideration at the time. The current usage of more complete retention functions removes some of this extra conservatism while still being realistic for the long-term situation. (See ICRP Publication 30 and Appendices, ICRP 1979.)

A paper by Morgan, Tipton, and Cook (1959) contains a general summary of many of the biological data used. This Oak Ridge work, given at the second Atoms for Peace Conference, emphasizes many of the biological decisions that entered the picture, in addition to the metabolic data.

With reference to metabolic data, the following points, among others, emerge:

1. The spectrographic analyses for stable elements showed marked geographical variation in some cases. This applied more to elements like cadmium, lead, and chromium than to essential elements such as calcium, iron, zinc, copper, manganese, etc.
2. Other elements showed marked variation with age of the subject e.g., copper and zinc in liver, aluminum in lung, and cadmium in kidney.
3. It was frequently necessary to extrapolate not only from animals to humans, but from the distribution associated with a single intake to that applying to multiple, long-term intakes.

Apropos this last point, it is not easy to find experiments designed specifically to compare the metabolism of isotopes acquired in single compared to multiple doses. In chapter 4, we reviewed work by Stannard and colleagues using rats maintained at a more or less constant body burden of ^{210}Po . There were significant differences in distribution compared to a single dose. The biological half-life was longer, the tissue distribution remained throughout the lifetime closely similar to that at short times after a single injection. There was much less redistribution with time. This is not surprising since it was always no more than one month since the last injection.

We saw in chapter 9 that many of the inhalation exposures continued over many years. This was particularly true of the uranium work at Rochester. Since there was also early data after single exposures, a valid comparison of the two modes could be drawn. However, not much point was made of this comparison in the standard-setting process. Instead, since the bulk of the data resulted from long-continued or at least multiple inhalation exposures, these tissue distribution figures were used more or less as they came out. It is almost impossible to determine which mode prevailed in some cases. Except for inhalation exposures, and of course the exposures of man, the single exposure mode predominated.^(a,b)

(a) Recently, this question has been formally reviewed by the Lovelace group (see chapter 9). Diel and Lundgren (1982) measured whole-body retention and distribution of ^{239}Pu in selected tissues of beagle dogs after a series of two or four inhalation exposures (at half-year intervals) and compared them to those following a single exposure. The experiments indicated that each exposure behaved essentially independently of the others. The authors cite one human case with repeated inhalation exposures to plutonium-uranium fuels. The same picture was evident (Ramsden, Bains, and Fraser 1978). By contrast, repeated inhalation exposures to $^{144}\text{CeO}_2$ in mice and ^{137}Cs particles in dogs indicated greater retention in the lungs (Boecker, Thomas, and McClellan 1977; Lundgren et al. 1980). The authors speculate that longer-range radiation from ^{144}Ce produced progressive lung damage, which interfered with clearance processes.

(b) The analysis in NCRP 1985a mentioned earlier also addresses this point.

The internal emitter dosimetry people at Oak Ridge, with help from Marquette University, devised an experiment specifically to test the practice of using single exposure data for calculating MPCs in water for continuous exposure (Cook, Morgan, and Barkow 1956). They chose ^{60}Co and found very little difference in its distribution between single and multiple doses. This result seems to have led to the conclusion in the internal dose committees that the practice was not fraught with serious difficulties.

At the time of the development of "the system," there were few alternatives. However, there is now much information that could contribute to a valid comparison of single and multiple dose kinetics. This information has never, so far as is evident, been assimilated overtly into modified calculations by the recommending bodies. It is doubtful if anyone has been harmed by this omission, but it seems to have been ignored; at least it is seldom mentioned in the standard-setting process in the later years. It was incorporated into EISs and appears to have been considered in the development of the data for specific isotopes in the reports of the late 1970s. The significance, if any, of this hiatus is not addressed to the extent that it should have been.

On the other hand, the recent publications (especially ICRP 30 with its voluminous appendices) give ample and specific information that should allow detailed tracing of the data used in each case and provide a basis for modifications if such are needed. Indeed, the volume of material is so large that it seems doubtful if another such effort would be needed for at least a decade. Only the honing of estimates of risk (see later section) appears to be essential.

B. Metabolic Models

The simple assumptions described above might be regarded as technically metabolic models since a single generalization was applied to a large number of radionuclides, tissues, and organs. However, there were different figures for each situation. Still more generalized schemes were developed. It is these that we will consider in this section and in section VI.

1. Biokinetic Model

The assumptions applied in the 1959 NCRP/ICRP reports for metabolic behavior of the elements were replaced in 1979 (ICRP Publication 30) by a systemic biokinetic model utilizing several compartments. It was applied, with a few exceptions, in all of the dose calculations. The basic model is shown as figure 16.4.

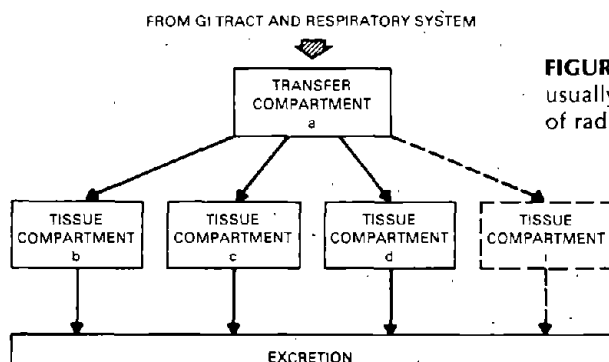


FIGURE 16.4. Mathematical model usually used to describe the kinetics of radionuclides in the body; exceptions to this model are noted in the metabolic data for individual elements. (Redrawn from ICRP 1979. Reprinted with permission of Pergamon Press, Elmsford, New York, copyright 1979.)

It is immediately apparent that this is more like the compartmental models used generally in physiology and pharmacology. The first compartment, (a), is intended to cover the time taken for translocation from the site of entry into body fluids for transfer to the various tissues. This is assumed to have first-order kinetics to time (i.e., a single exponential) with a half-life of 0.25 days unless otherwise stated. Each organ or tissue is assumed to have one or more compartments into which the radionuclide settled and was subsequently translocated elsewhere or to the excretion pathway. The release rate takes into account both the clearance rate into the compartment from the transfer compartment and the respective losses of the *stable* isotopes of the element from the compartments b, c, d, etc. A factor for radioactive decay of the radionuclide is then added.

This model is obviously more complex than the one utilized by NCRP/ICRP in 1959. Yet, it hews to the line of using exponential kinetics (by way of decay constants). It has been criticized by some because there are no terms for feedback, i.e., movement in the direction opposite to the arrows, a normal physiological process. Those who developed the model were aware of this and caution that estimates of dose along the route of excretion should not be attempted from this model. The final result is probably not significantly influenced by the omission of feedback. The constants used are, fortunately, derived from the biological data. The rates measured are already *net* rates, *including feedback*. Details of the equations used can be seen in ICRP Publication 30, Part I, p. 18 (ICRP 1979).

The origin of this model cannot be pinpointed to any single group of workers, even to any single country. It simply appeared as a result of the ICRP Committee II's efforts. Since it is much like the families of compartmental models used throughout physiology and pharmacology, there is probably little need to establish its origin or attempt to give credit.

2. Bone Model

A very large effort has gone into dosimetric models for bone. These are described in ICRP Publication 30 and, with more historical perspective, in the NCRP report cited earlier (NCRP 1985a). They are also considered briefly in chapter 20. Space does not permit detailed discussion. We should remark, however, that no single tissue has received as much research attention, or had so many schemata developed around it, as has bone. That should be obvious from the earlier chapters.

The only complete generalized and self-contained *metabolic* model (as compared to *dosimetric* model) is the one developed for the behavior of the alkaline earth elements in bone. This was the result of much hard work by a special task group of ICRP Committee II chaired by John H. Marshall of ANL. It was adopted by the Commission in May 1972 (the task group was organized in 1968), and it has come to be known as "The Marshall Model." It was published as ICRP Publication 20 and also, after peer review, in the journal *Health Physics* (ICRP 1973).

A very abbreviated summary of this model is given as note 4 at the end of this chapter.

The report contains much more than a model. It is a fine summary of much of the biokinetic data for important bone-seeking radionuclides in the body. Despite its ninety-two pages, a plea is made at the end for more data. These include bone surface data and soft tissue data for the heavier alkaline earths,

the relative activity in new and old bone, more data on ^{90}Sr in human bone, and information on rates of resorption in the radium cases.

The other members of the task group were J. Liniecki, E. L. Lloyd, G. Marotti, C. W. Mays, J. Rundo, H. A. Sessions, and W. S. Snyder. Acknowledgments were made to R. E. Rowland, R. C. Thompson, J. Vennart, and P. Groer, the last for review of the mathematics.

It is a commentary on the difficulty of the task that no comparable generic model has yet been developed for the all-important actinide elements in bone. Nor have generalized models been developed for other tissues, except for lung and gastrointestinal tract, as we will see in the next section. There have been numerous models for specific elements. An early one was developed for hexavalent uranium by Struxness and colleagues at Oak Ridge (Struxness et al. 1956). A revised and updated model is being developed by Wrenn, Roswell, and Durbin (1982).^(a) Many animal models have been made for plutonium; environmental models for iodine, etc.; but these are not as close to the standard-setting process as those we have been discussing.

It seems possible that a generic model for actinides in bone may be "just around the corner." At the 1979 meeting on actinides in man and animals, an entire section was devoted to metabolic mobility of actinides. The Battelle group presented a comparison of plutonium metabolism and pulmonary tumors in dogs and rats (Mahaffey et al. 1981). Skrable and his colleagues at the University of Lowell (Massachusetts) described retention functions in general (not just for actinides) and summarized current models for the actinides applicable to radiation protection (Skrable, Chabot, and Johnson 1981).^(b) A comparison is made of the ICRP Publication-2 model, the ICRP Publication-30 model, a mammillary model, and one involving blood-organ transfer kinetics. Bernard, a long-experienced modeler for the Oak Ridge group, presented what has been termed an "Urn" model for plutonium. The term comes from the concept of a container (i.e., an urn) holding different colored balls and representing an organ of the body containing different atoms (Bernard 1981). In the final paper of the session, Cuddihy (Lovelace Foundation) addressed actinide modeling in both bone and liver with the conclusion that newer laboratory data do not support current ICRP models (Cuddihy 1981). However, this is not surprising since the ICRP model was developed to assure protection of workers, and this was conservative in a number of aspects.

These models are hardly simple. Also, it may be that the new work will tear apart the model already in place for alkaline earths rather than add one for actinides. Only the future can tell. Nature guards her secrets zealously!

VI. Other Models

A. Lung Model

One of the most urgent needs in the early development of standards for radionuclide uptake was one for the behavior of particles and gases in the respiratory tract. As discussed in earlier chapters, many assumptions appeared in the

(a) It was published in 1985 (Wrenn et al. 1985), and expanded upon by Durbin (1986).

(b) Kenneth Skrable has risen rapidly to be currently one of the most active and prolific developers of the mathematical aspects of internal dosimetry.

MED days in connection with the behavior of particles and gases in the respiratory tract. These were usually part of a consideration of a specific situation and specific radionuclides. We also saw, particularly in chapter 9, the broad extent to which the influence of particle size was researched, both during and after the war years.

At the Tri-Partite Conferences on Permissible Doses, various individuals gave information on behavior in the respiratory tract of the radionuclides they had been working with. Gradually some generalizations emerged. By the time of the third Tri-Partite Conference, held at Arden House, Harriman, New York, a scheme was proposed and adopted that became the first general lung model.

This early model is shown in table 16.2A. While the scheme is said to have been put forward by Morgan and Eisenbud^(a) (Taylor 1984), it is clear that there was input from Brues, Bugher, Cipriani, Hamilton, Marinelli, and Mitchell. Also, it is hard to believe that Wright Langham was not furthering the enterprise in view of his long-standing interest in inhalation problems.

TABLE 16.2A. Early Lung Model

	Soluble Compounds	Insoluble Compounds
Exhaled	25%	25%
Deposited in upper respiratory passages	50%	50%
Deposited in lungs	25% (This is taken up into the body)	25% (Of this, 15% is eliminated in 24 hours, 10% remaining in the lungs indefinitely)

Source: Reset from minutes of Third Tri-Partite Conference, Taylor 1984, Appendix 23.

A very similar model appeared in the 1959 ICRP report. It is reproduced as table 16.2B. It will be noted that the principal difference is in the retention behavior of insoluble compounds in the lower respiratory passages. Later still, the retention half-times for thorium and plutonium were increased to three hundred days.

It will be noted that neither model says anything about particle size or its influence. They were simply assumed to apply to the average respirable aerosol. Likewise, chemical form was marked only as "soluble" or "insoluble." There was more discussion at the Tri-Partite Conferences of the differences between nose and mouth breathers than the differences due to particle size! This was indeed painting with a broad brush, but it met the needs of the time for devising standards.

It was recognized that these models were too crude for permanent use, indeed that much more information could be applied relatively soon.

(a) This was when Merrill Eisenbud was at the New York Operations office of the AEC. He was deeply involved with industrial hygiene aspects of all AEC operations, particularly those involving uranium.

TABLE 16.2B. ICRP Publication 2 Lung Model*Particulates in respiratory tract of the standard man*

Retention of particulate matter in the lungs depends on many factors, such as the size, the shape and density of the particles, the chemical form and whether or not the person is a mouth breather; however, when specific data are lacking it is assumed the distribution is as shown below.

Distribution	Readily Soluble Compounds (%)	Other Compounds (%)
Exhaled	25	25
Deposited in upper respiratory passages and subsequently swallowed	50	50
Deposited in the lungs (lower respiratory passages)	25 (This is taken up into the body)	25*

*Of this, half is eliminated from the lungs and swallowed in the first 24 hours, making a total of 62½ per cent swallowed. The remaining 12½ per cent is retained in the lungs with a half-life of 120 days, it being assumed that this portion is taken up into body fluids.

Source: Reset from ICRP 1959, p. 153. Reprinted with permission of Pergamon Press, Elmsford, New York, copyright 1959.

Consequently, in 1964, the ICRP appointed a special task group under Committee II, the Task Group on Lung Dynamics (TGLD), to devise a more sophisticated model. Respiratory tract parameters, transport functions, and the effect of particle size were all studied in depth. The group was chaired by Paul E. Morrow, University of Rochester, an outstanding respiratory physiologist-pharmacologist. Other members were: David V. Bates, Royal Victoria Hospital, Montreal; Birney Fish, Oak Ridge National Laboratory; Thomas T. Mercer, University of Rochester; and Theodore F. Hatch, University of Pittsburgh. Consultants and special contributors were Drs. Donald A. Morken (University of Rochester); G. Parry Howells (U.K., Belmont, Surrey); J. Rundo (U.K., AERE Harwell); Dr. Halloway (Oak Ridge); and Messrs. W. Downs, L. Leach, A. Raabe and Mrs. Léon Greenwold, all at the University of Rochester at the time.

As mentioned in chapter 9, the new model was a quantum jump from the 1959 version. The first report appeared as a journal publication in 1966 (TGLD 1966), record time for such a complex venture. Deposition is addressed as a function of particle size in three major divisions of the adult human respiratory tract—naso-pharyngeal (N-P), tracheobronchial (T-B), and pulmonary (P). The lymph nodes and lymph are considered as a depository separate from the respiratory system. Clearance constants are provided for three major classes of compounds divided according to duration of retention in the lung (see below) for each of the major components, as well as constants for translocation to body fluids and lymph nodes.

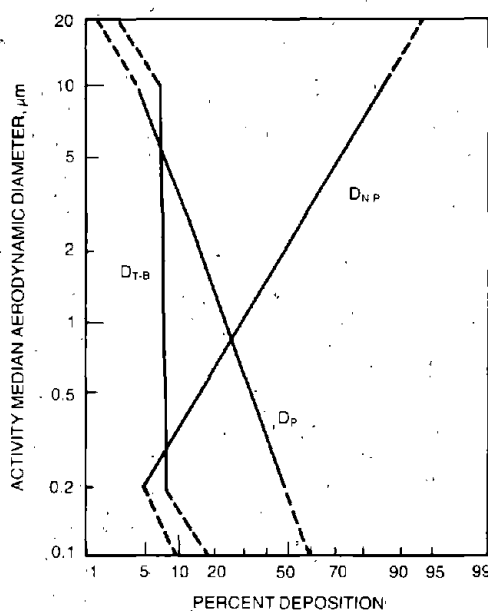
The model was an instant success. It began to be used immediately, albeit informally, in calculations of the day. It was especially useful for the numerous EISs being developed at the time. It was quoted, with slightly modified

clearance constants, in ICRP Publication 19, which concerned plutonium (ICRP 1972). However, since this was a blue covered book, by ICRP convention the model's inclusion there was not an official adoption or recommendation. This had to await the publication of the official document on *Limits for Intakes of Radionuclides by Workers*, i.e., Publication 30, in 1979.

The "official" model as described in ICRP Publication 30 has the usual updating of certain constants but incorporates the fundamental plan worked out by the task group. Deposition was shown as a function of particle size (activity median aerodynamic diameter [AMAD]) for the three regions of the respiratory tract. It applied to aerosols of AMAD between 0.2 and 10 μm .

The clearance functions were drawn from a compartmental model using deposition values for an aerosol of 1 μm AMAD. The basic features of these schemes are shown in figure 16.5A and B. The text of the ICRP report gives all of the equations necessary for each step as a series of first-order, interlinked, differential equations.^(a)

FIGURE 16.5A. Deposition of dust in the respiratory system. The percentage of activity or mass of an aerosol which is deposited in the N-P, T-B, and P regions is given in relation to the Activity Median Aerodynamic Diameter (AMAD) of the aerosol distribution. The model is intended for use with aerosol distributions with AMAD between 0.2 and 10 μm and with geometric standard deviations of less than 4.5. Provisional estimates of deposition further extending the size range are given by the dashed lines: For an unusual distribution with an AMAD of greater than 20 μm , complete deposition in N-P can be assumed. The model does not apply to aerosols with AMADs of less than 0.1 μm . (Redrawn from ICRP 1979. Reprinted with permission of Pergamon Press, Elmsford, New York, copyright 1979.)



The only major differences between the 1966 and 1972 versions and the one in ICRP Publication 30 are as follows: (1) the dose to the N-P region was considered so small that it could be neglected; (2) the T-B, P, and L regions were combined into a single target tissue with a mass of 1,000 g. The latter was done because of the problems of deciding which region to use for dose calculation and uncertainties concerning the location of the cells at most risk.

The former is not acceptable to many investigators. The nasopharynx is a demonstrated site of origin of cancer from inhaled substances. Many do not

(a) For the convenience of the reader not having access to ICRP documents, they are reproduced in the 1985 NCRP report cited earlier (NCRP 1985a).

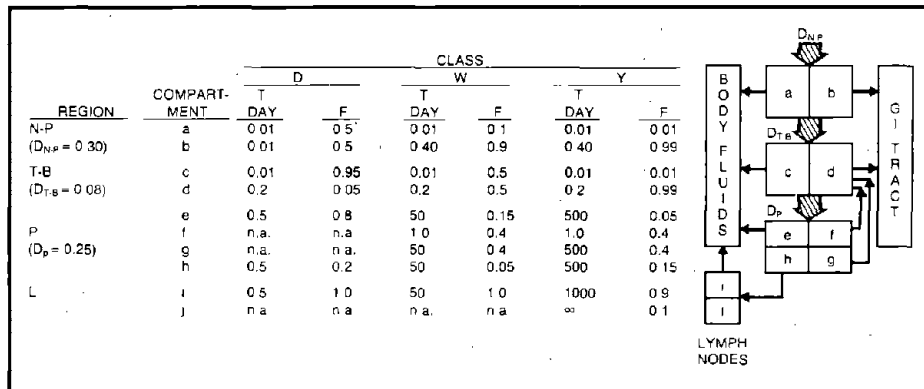


FIGURE 16.5B. Mathematical model used to describe clearance from the respiratory system. The values for the removal half-times, T_{a-j} and compartmental fractions, F_{a-j} are given in the tabular portion of the figure for each of the three classes of retained materials. The values given for D_{N-P} , D_{T-B} , and D_P (left column) are the regional depositions for an aerosol with an AMAD of 1μ . The schematic drawing identifies the various clearance pathways from compartments a-i in the four respiratory regions, N-P, T-B, P and L. n.a. = not applicable. (Redrawn from ICRP 1979. Reprinted with permission of Pergamon Press, Elmsford, New York, copyright 1979.)

consider the dose to this region as always negligible. Work with chemical toxicants confirms this view. Furthermore, the lumping of the major compartments is not universally considered as better than the 1966 version.

Also, the particle size range in the original model was 0.01 to $100 \mu\text{m}$ AMAD. The reduced range in the official model (0.1 to $10 \mu\text{m}$) probably reflects the difficulties of obtaining good data below $0.1 \mu\text{m}$ AMAD and the unimportance of particles above $10 \mu\text{m}$.

It is important to realize that the clearance model is not tied irretrievably to a particle size of $1 \mu\text{m}$ AMAD as given in the legend to figure 16.5B. The H_{50} (committed dose equivalent for fifty years) can be adjusted from the calculated values given in the supplements to ICRP Publication 30 by using the following relationship:

$$\frac{H_{50}(\text{AMAD})}{H_{50}(1 \mu\text{m})} = f_{N-P} \frac{D_{N-P}(\text{AMAD})}{D_{N-P}(1 \mu\text{m})} + f_{T-B} \frac{D_{T-B}(\text{AMAD})}{D_{T-B}(1 \mu\text{m})} + f_P \frac{D_P(\text{AMAD})}{D_P(1 \mu\text{m})}$$

where D_{N-P} , D_{T-B} , and D_P are the deposition probabilities in the respiratory regions for a given AMAD shown in figure 16.5A and f_{N-P} , etc., refers to the fraction of committed dose equivalent resulting from deposition in the named compartment.

Not shown in the official version of the model is the detailed tabulation of biological half-lives determined in many species for many chemical forms of a large number of elements, along with recommended values for many elements under single or multiple exposure regimes given in the 1966 publication. Also, the pulmonary clearance classifications were given in detail there for various inorganic compounds: carbides, sulfides, sulfates, carbonates, phosphates, oxides and hydroxides, halides, and nitrates with enumeration of those elements

whose compounds fell into each of the three major clearance classifications, i.e., Class D, minimal retention (days); Class W, moderate retention, intermediate clearance (weeks); and Class Y, avid retention, slow clearance (years). The serious student of lung models needs to study this information from the 1966 report to understand the classifications used in the new ICRP report and model.

This model is applicable not only to aerosols of radioactive materials, but to any aerosol. With small modifications, it could, and *should* be used in routine industrial hygiene practice. It is an invaluable contribution to the entire field.

We can expect modifications in detail as forecast in the recent NCRP report (NCRP 1985a), and from new task groups of the NCRP and ICRP. New research in this field is going on particularly at the Lovelace Foundation and at Battelle (see chapter 9).

B. Gastrointestinal-Tract Models

Next to respiratory-tract parameters, some of the most important figures in the development of standards concern the gastrointestinal tract. Before doses could be calculated, and before it could be ascertained whether or not a section of the gastrointestinal tract might be considered as a critical organ, decisions needed to be made regarding its characteristics. The question of what mass to use for the gastrointestinal tract and the mass of the contents was discussed briefly at the Tri-Partite Conferences. The data for "standard man" (see next section) gave figures for a "present ICRP value" of 2,000 and 2,300 g, respectively (Arden House meeting). However, this was not in the detail needed. Suggestions for rate of passage as well as weights of the contents of different portions of the gastrointestinal tract came from the United Kingdom. Sir Edward Pochin sent a proposed model for these to Karl Morgan by letter in October 1953. In the interim between 1954 and 1959, the members of NCRP/ICRP Committees II drew together the information and came up with a fairly detailed description of the gastrointestinal tract, which appears in the 1959 ICRP report, as shown in table 16.3 below.

TABLE 16.3. Gastrointestinal Tract of the Standard Man

Portion of GI Tract that is the Critical Tissue	Mass of Contents (g)	Time Food Remains, τ (day)	Fraction from Lung to GI Tract, f_a	
			(sol.)	(insol.)
Stomach (S)	250	1/24	0.50	0.625
Small intestine (SI)	1100	4/24	0.50	0.625
Upper large intestine (ULI)	135	8/24	0.50	0.625
Lower large intestine (LLI)	150	18/24	0.50	0.625

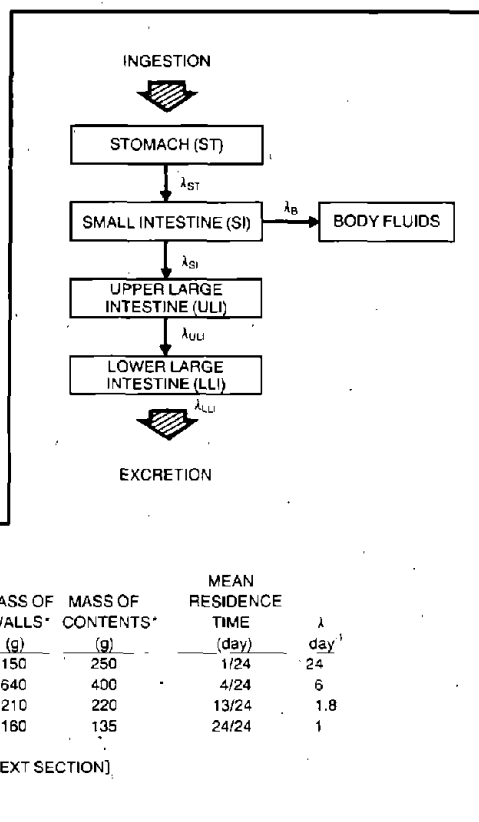
Source: Reset from ICRP 1959. Reprinted with permission of Pergamon Press, Elmsford, New York, copyright 1959.

In the interim between the "old" ICRP/NCRP report (i.e., 1959) and the "new" ICRP report (1979), two important contributions came from the United Kingdom. Eve (1966) reviewed the physiology of the gastrointestinal tract in relation to doses from radioisotopes, and Dolphin and Eve (1966) summarized the relevant dosimetry.

For the new ICRP internal emitter report (ICRP 1979), a compartmental representation was added, along with slightly different figures for mass and residence times. Also, the complete dosimetric model, with equations for each step, was developed in the text. This includes activity transferred to the gastrointestinal tract from the respiratory system, as well as outward transfer to body fluids and excretion.

The model and constants are shown in figure 16.6.

FIGURE 16.6. ICRP model for kinetics of radionuclides in gastrointestinal tract. (Redrawn from ICRP 1979. Reprinted with permission of Pergamon Press, Elmsford, New York, copyright 1979.)



Not shown in the model is the fact that a factor between zero and one is applied in the calculations depending upon the penetration characteristics of the radiation from each radionuclide. Many radiations penetrate the mucus layer of the gastrointestinal tract only with difficulty, as well as being absorbed to a considerable extent in the gut contents. In the absence of specific information to the contrary, the factor is taken as unity for photons and beta particles, 0.01 for alpha particles and fission fragments, and as zero for recoil atoms. Without this factor, doses to the gut wall for radiations of low penetrability would be grossly overestimated.

The cited NCRP report (1985a) points out that the proliferating cells in intestinal crypts, which are probably the most important potential target cells, are not at the interface between intestinal wall and intestinal contents. They are approximately 1,000 μm within the intestinal wall. For low-energy radiations and those with low penetrability, the assumption that the critical cells are at the interface lends considerable conservatism to the model. A second important feature of the behavior of radionuclides in the gastrointestinal tract is their absorption rate. This figures in all of the calculations for MPC in water. It also figures in all of the annual limits on intake by the oral route using the NCRP/ICRP

system. The factor, f_w in the 1959 system, f_1 in the 1979 system, is idiosyncratic for each element. It probably varies also with the chemical form ingested.^(a)

Most of the values used in the 1959 reports were based on gut absorption in animals given the radionuclide in the fasting state by the process of gavage. We have discussed the pitfalls of this methodology in earlier chapters. However, there was not much else to use at the time of the earlier calculations.

With the advances of internal emitter research, values for humans became more regularly available. The data came from measurements of the absorption of the radionuclides in fallout by dietary intake (chapters 12 and 13) and experiments on volunteers (chapters 13 and 20). These were applied as feasible.

A center for research activity on gastrointestinal absorption of various radionuclides has existed at Battelle, Pacific Northwest Laboratories. M. F. Sullivan has essentially spent a career on the subject with a series of collaborators.^(b) Typical information generated can be seen in a review directed at the actinide elements prepared as an "in-house" document and later published (Sullivan 1978, 1980, 1981). This contribution delved further into the influence of chemical form and indicated that "soluble" and "insoluble" compounds of the actinides were *both* poorly absorbed from the gastrointestinal tract. The work also demonstrated little difference among the species for americium and plutonium, much greater variation in the rat for the other elements used, but not in dog or guinea pig.

Nearly every laboratory doing metabolism of internal emitters made its contributions to the figures for gastrointestinal absorption, as seen in earlier chapters. Special mention should be made of the ongoing studies at ANL (Larsen et al. 1981). This group examined the solution chemistry of plutonium and other actinides with reference to gastrointestinal tract absorption. A marked influence of valence state was described.

An important perturbation, alluded to earlier, appeared in some of this work. For some elements at least, the fractional absorption appeared to increase as the absolute concentration decreased. Thus, at the low concentrations associated with environmental and population exposure, fractional absorption could be considerably greater than at the higher levels used in the gavage experiments. This was especially noted for uranium in work of Durbin at the University of California, Berkeley, and later by Wrenn at Utah and New York University. In fact, the relationship was regular enough to be graphed in a discussion of the subject at the Snowbird actinide symposium in 1979 (Wrenn 1981). The work presented is part of a current joint effort by Durbin and Wrenn.^(c)

It will be noted in figure 16.7A that much of the relationship depends on a single point (average) at the lowest concentration ingested. Because of the importance of such relationships to setting standards for drinking water, the EPA asked that it be reviewed at a National Workshop on Radioactivity in

(a) This complication is sidestepped in part by reasoning that chemical forms that are different on entrance merge to a more common form by reactions in the gut. Thus, only "soluble" and "insoluble" are distinguished.

(b) Much work from the old Hanford Laboratories bears on this subject also, as mentioned in chapters 6, 7, and 8. The names of J. Ballou, V. H. Smith, and R. C. Thompson should be looked for.

(c) The relationship was described first by Durbin in an unpublished manuscript mailed to members of NCRP Scientific Committee-34 (Durbin 1976). It has become less obvious with further work, as described.

Drinking Water convened in May 1983. The results were published as a special issue of *Health Physics* (Vol. 48, No. 5, 1985). In it, Wrenn and six collaborators, including Durbin, reviewed most of the extant data on metabolism of ingested uranium and radium (Wrenn et al. 1985). This included a redo of the relationship between uranium uptake from the gastrointestinal tract and the intake in $\mu\text{gU/kg/day}$. The result is the graph shown as figure 16.7B. There is still a suggestion of the relationship shown in figure 16.7A, but the slope is less steep, and the data from rats indicate hardly any effect at all.

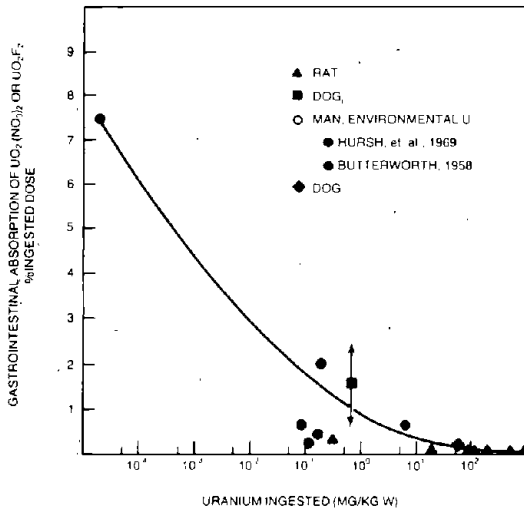


FIGURE 16.7A. (Left) Effect of concentration on gastrointestinal-tract absorption of uranium. (Redrawn from Wrenn 1981. Reprinted with permission of RD Press, University of Utah, Salt Lake City, Utah, copyright 1981.)

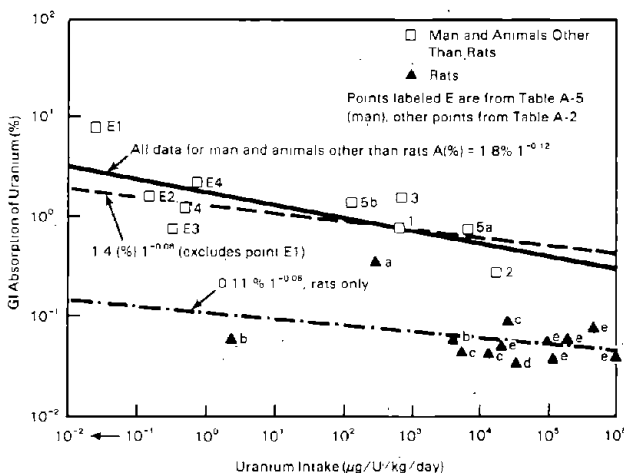


FIGURE 16.7B. (Below) A later plot of gastrointestinal absorption of uranium plotted as a function of intake. Details of the symbols can be found in the original reference. They pertain to the origin of the figures. Experiments in which the concentration of U ingested was more than $10^3 \mu\text{gU/kg/day}$ were omitted in fitting the curves, since they appear unlikely to be encountered in environmental exposures, which was the primary thrust of this work. (Graph redrawn from Wrenn et al. 1985. Reprinted with permission of Pergamon Press, Elmsford, New York, copyright 1985.)

It was thought for a while that this phenomenon might be a general one. However, examination of data for other radionuclides, e.g., plutonium, indicated more or less invariant absorption at different intake concentrations (Harrison et al. 1981). It may well be that differences among radionuclides, if they do occur,

could reside in differences in specific activities, but dietary factors appear to be of importance also (chapter 15).

Some new, higher gastrointestinal absorption figures found their way into the f_1 values used in ICRP Publication 30 and Supplements. They can have a large effect on exposure standards.

There is also the problem of the large range of values for gut uptake. Harrison (1981) at the NRPB in the United Kingdom has addressed this subject for inorganic actinide compounds. The ICRP (1979) value and the range of experimental results are shown in table 16.4, taken from the Harrison paper.

TABLE 16.4. Gut Uptake Values Recommended by ICRP for Occupational Exposure to Inorganic Actinide Compounds Compared to Experimental Results

Actinide	ICRP Value % Absorption	Experimental Results	
		% Absorption	Species
Thorium	0.02	0.005—1	Rat, guinea-pig, human
Protactinium	0.1	0.006—0.2	Rat, hamster
Uranium*	5	0.06 —5	Rat, hamster, dog, human
Neptunium	1	0.05 —1.5	Rat, hamster
Plutonium*	0.01	0.001—0.1	Mouse, rat, hamster, guinea-pig, rabbit, pig, dog
Americium	0.05	0.006—0.1	Rat, hamster, guinea-pig, rabbit
Curium	0.05	0.003—0.1	Rat

*Both U and Pu are assigned values for more soluble and less soluble forms; the values given are for the more soluble forms.

All results given are for inorganic compounds of the elements in normally fed adult animals.

Source: Reset from Harrison 1981. Reprinted with permission of the National Radiation Protection Board, Oxon, England, copyright 1981.

Some of this range may be due to differences in concentration in the gut, and thus to the phenomenon described for uranium above, but how much cannot be determined from the data. Only a systematic investigation of many important elements at many intake concentrations can sort out how much of "biological variability" is due to one cause over another.

In addition, there are the usual effects of age and diet on gastrointestinal uptake of various elements. A recent summary for the actinides can be found in the paper by Harrison (1981).

It might seem that figures for gastrointestinal uptake would be among the easiest to come by. Recent experience shows that this is not true and that the use of single values is a very great simplification. Furthermore, the choice of figures sometimes makes a very large difference in the applicable standards. Already some of the uptake figures chosen for ICRP Publication 30 have had to be re-examined. There is a spate of new work that must continue to completion if we are not either to spend millions of dollars with unnecessarily low guidelines or apply a mistakenly high guideline and thereby produce biological damage. We need to get much more serious about the role of chemical form for each major radionuclide and for each class of radionuclides.

C. Reference Man (Standard Man)

The development of Reference Man began too at the Tri-Partite Conferences. At the first conference in Chalk River, Ontario, it was considered essential to formulate a set of biological parameters for both internal and external radiation exposures. Naturally, some parameters had already come into common usage, but it was agreed that without a carefully specified set of values the biological basis for published standards would have to be presented each time. If they differed, the standards might differ in an uncontrolled manner. Each health physicist would have to begin "ab initio"^(a) in every instance. Also, any adjustment of values to meet the needs of special situations would not have a known base line from which to work.

External radiation standards needed only fairly simple specifications of organ mass, dimensions, and elemental composition. For the calculation of permissible levels for radionuclides, much more was needed, including the mass of many more organs, more details of the chemical composition of organs and tissues, patterns of intake and excretion, water balance, respiratory parameters, etc., some of which have already been described.

This collection of information became known as "Standard Man." Minutes from the Chalk River Conference contain the first specifications. Herman Lisco, a pathologist at the University of Chicago and ANL, and Mary Jane Cook, Oak Ridge National Laboratory, whom we met in chapters 7 and 8, supplied data for the mass of organs. Chemical composition of the total body and various tissues was taken from a standard textbook of physiological chemistry of the day (Hawk, Oser, and Somerson 1947).^(b)

There were modifications at the later Tri-Partite Conference at Harriman House and at the Sixth and Seventh International Congresses of Radiology. An agreed-upon set of characteristics for "Standard Man" appeared in the 1954 and 1959 reports of the Internal Dose Committees of NCRP/ICRP. This was the work of the committees, and no special group was designated as responsible in the reports.

We will make no attempt to give details here. It should be emphasized, however, that the figures are not averages or medians of any specified population group. Judgment was used in the selection to try to present values that would be most likely to represent a typical individual of the European or American population. Since these are heterogeneous populations, the figures do not reflect ethnic or regional populations. Nevertheless, on balance, "Standard Man" could be regarded as weighing 70 kg, being 170 cm high, between twenty and thirty years old, a Caucasian of Western European habit or custom and living in a climate with an average temperature of 10° to 20°C.^(c) "He" was used for calculation of the MPC and other values in the 1954 and 1959 NCRP/ICRP reports.

The extent to which judgment, rather than purely statistical factors, entered into the decision is apparent from the minutes of the Tri-Partite Conferences. Somewhat amusing are statements agreeing that the weight of a given organ is

(a) Term used by ICRP in the report to be cited.

(b) This was, of course, before the large-scale investigations by Tipton referred to in section IV.

(c) Much colder or warmer climates would have considerable influence on water intake and diet.

so many grams. The committees were, of course, fully aware of the wide range of values which might occur. But they did not confuse things by putting ranges on their chosen values. They simply devised a standard man and advised anyone with knowledge that his situation differed markedly from the standard to use his own values. Since the calculations were used mostly for prospective evaluations and the setting of general standards, there were few takers of this proffered flexibility.

This work was greatly expanded by the appointment of a special task group of ICRP. The circumstances and charge can be seen by a quotation from the book-length report produced by this task group:

In December of 1963, Committee II of ICRP requested that the Commission establish a Task Group for the revision and extension of the standard man concept. At the suggestion of the Commission, the name was changed later from "Standard" Man to "Reference" Man. The charge to the Task Group on Revision of Reference Man was in the following terms:

Estimates of dose equivalent resulting from human exposure to radionuclides that may enter the body depend upon many characteristics which must be indicated clearly if the Commission's recommendations on dose commitment, body burden, and MPCs are to be applied correctly. For this reason the Commission's recommendations relating to dose equivalent from internally deposited emitters have been specified in terms of a "Reference Man" whose characteristics, so far as relevant to the Commission's recommendations, are carefully specified. Because of the increased emphasis on exposure of the population, it is desirable that the specifications of the previous Standard Man be reviewed and revised to take account of present needs for evaluation of exposure to radiation.

The task group should review those characteristics of man that relate directly or indirectly to intake, metabolism, distribution in the body, and retention of the various isotopes of concern. In particular, it is desired to define Reference Man, in the first instance, as a typical occupational individual, and it is important that some indication of variability of the occupational group about this norm be indicated. In addition, differences due to age, sex, or habits should be indicated where possible with particular emphasis on fetuses, infants, and children.

It is expected that a separate task group will consider the problem of devising a lung model, and thus the Task Group on Reference Man need not consider the mechanism of inhalation, deposition, or lung retention. It is expected also that some independent assistance on the gastrointestinal tract will be available but that this will be offered to the task group directly.

It is clear that the work involves two aspects: (1) the revision and extension of a Reference Man which represents a typical radiation worker, and (2) extension of the concept to give an indication of the extent of individual variation among grossly normal individuals and to include dependence on age, sex, and to some extent other factors whose effects must be considered in estimating dose to individuals of the population. (ICRP 1975)

The members of the task group were:

W. S. Snyder, U.S., Oak Ridge, Chairman
 M. J. Cook, U.S., Oak Ridge
 L. R. Karhausen,
 E. S. Nasset, U.S., Rochester and later in retirement, Berkeley, CA
 G. Parry Howells, U.K., Belmont, Surrey
 I. H. Tipton, U.S., University of Tennessee and Oak Ridge.

Primary responsibilities were divided as follows: (1) anatomical values for Reference Man, a very large section which included many physiological and

biochemical parameters along with conventional anatomical values (L. Karhausen);^(a) (2) elemental composition of tissues and the whole body (I. H. Tipton); (3) intake and excretion (G. Parry Howells); (4) literature referencing, cross-checking, editing and indexing (M. J. Cook); and (5) physical data on dosimetry and final editing (W. S. Snyder). E. S. Nasset contributed first as a consultant and then as a member of the task group. Nasset was an expert in nutrition and gastrointestinal physiology and probably contributed especially to these aspects, as well as to the overall product.

The final publication is a closely knit volume of 480 pages, with over 130 tables, not counting summary and addendum. Despite this, the task group emphasizes that *only* characteristics significant for estimating radiation doses are included. There was no attempt to embody "all known characteristics of man." For this, the reader would need to turn to the multivolume comprehensive *Handbook of Physiology* published by the American Physiological Society over a period of years (APS Handbook).

The ICRP Reference Man report has a summary of model values for fifty-one elements and an appendix showing Specific Absorbed Fractions of Photon Energies for Reference Man (see chapter 20). It met its purposes admirably and supplies continuously most of the basic data needed for the computational approach to standard setting. Nevertheless, as recognized by the ICRP and others, applications to population standards require more information on infants and children and more information on non-Caucasian groups. These are being produced gradually. The Japanese have already published a version of reference man more applicable to their anatomical and dietary characteristics (Tanaka, Kawamura, and Nakahara 1979; Tanaka, Kawamura, and Nomura 1981). However, these developments are beyond the scope of this history, except to mention them as a portent for the future.

The ICRP has recently announced appointment of a new task group, chaired by C. R. Richmond (Oak Ridge), to update and expand the model for Reference Man.

VII. Validation in Humans

In a sense, every experiment constitutes a validation or invalidation of previous work and/or of the hypotheses behind it. Here we are interested in research, primarily data from humans, that bears so directly on the processes or the input figures of standard setting that they could reflect on the validity of the standards themselves. The earlier phases bore primarily on validation of the metabolic models and the metabolic factors used. This still continues. Beginning early, but not bearing fruit until much later, are studies bearing on the presence or absence and the nature of biological effects.

In the United States, this work has been concentrated in only a few institutions (ANL, Hanford Environmental Health Foundation, and PNL [Hanford], Los Alamos, University of California, Berkeley). It is more convenient to structure the discourse around elements and general operating experience than around institutions, as we have done in some previous chapters.

(a) This section included total body; integumentary system; skeleton, cartilage, bone marrow, teeth, etc.; hematopoietic system; lymphatic system, spleen and thymus; skeletal muscle system; cardiovascular system; digestive system; respiratory system; urogenital system; endocrine system; central nervous system; special sense organs; and the characteristics of the components of pregnancy.

Since the standards for radium isotopes and for radon and its daughters were derived primarily from studies involving humans rather than indirectly, a formal validation process of the type to be presented in this section need not be described. The consistent failure to find bone sarcomas at levels below the maximum allowable, even with large increases in the size of the study groups for radium, was considered validation enough. Fortunately, the conservatism of the radium standard (see page 1413) was sufficient to encompass the incidence in later years and at lower radiation doses of carcinomas. Difficulties with the WL concept (see page 1416) make conclusions about the validity of the radon and radon daughter standards less than rock solid. Yet, even the most recent NAS-NRC analysis (NAS-NRC 1988), after a review of the epidemiologic data, comes up with estimates of lifetime risk of lung cancer mortality due to lifetime exposure to radon progeny within the range of earlier estimates.

A. Plutonium and the Transplutonic Elements

The largest validation enterprise by far concerns the isotopes of plutonium and to a lesser extent other transuranium elements for reasons that are now obvious.

1. The Eighteen Patients

The work with eighteen hospitalized patients done during World War II under the auspices of the MED was described in chapter 7 (see also Langham et al. 1950, 1980). The work was entirely directed toward metabolism of plutonium. This group remains one of the most important, since the administered dose is known accurately. The patients were at Strong Memorial Hospital, Rochester, New York, the University Hospital in San Francisco, the Billings Hospital in Chicago, and the Oak Ridge Hospital. The data, with addition of some long-term excretion figures from Los Alamos workers, were the basis for the equations used for over three decades to calculate body burdens and organ burdens of plutonium.^(a)

The first serious attempts at reevaluation of these data came from Patricia Durbin at the University of California, Berkeley. It started with a UCRL report (Durbin 1971) entitled, "Plutonium in Man: A Twenty-Five Year Review." One refinement was separation of data from patients with diseases that might modify circulation, iron metabolism,^(b) gastrointestinal and kidney function, etc., from those that could be viewed as normal in these functions. It was apparent that there were differences among the patients consistent with an influence of their medical problems. Therefore, a second refinement was added—individual analysis of the data from each patient. In addition, the original data were reviewed in the light of advances in analytical techniques and possible errors introduced by the old methods. Durbin added new data using occupationally exposed persons and animal experiments for comparison.

It became clear that "the original data were good and that the original analysis was sound. The new data from occupationally exposed persons and from animal experiments, and the use of the iron analogue, contributed more to understanding the old results than did the difference in analytical approaches. The initial tissue distributions, excretory patterns, and predictions of long-term

(a) See Langham equation, and Langham-Healy equation in chapter 7.

(b) By this time, the transport of plutonium in combination with transferrin, the iron complexing moiety, and the similarities of plutonium and iron had been established.

plutonium elimination presented here do not differ in substance from the original analysis . . . only in detail" (from Durbin 1971, pp. 94-95).

A major contribution of Durbin's analysis, besides the important validation of earlier work and models, was the construction of a more generalized metabolic model for plutonium in humans. This model included excretion equations that were the sums of exponentials rather than the power functions used in the Langham and Langham and Healy models.

Since the original report on these patients still remained classified (see chapter 7), Durbin rendered an additional service by giving pertinent information on each patient, without revealing identity.

The UCRL report was followed by a published review by Durbin. It was given at the 1972 conference of the Utah Project (see chapter 8) and was entitled, "Plutonium in Man: A New Look at the Old Data" (Durbin 1972). The review is replete with graphed metabolic functions showing data from sheep, dogs, and exposed workers, and where the points from the patients fit.

The conclusions differ slightly from those quoted from the 1971 report. There is careful analysis of the forms of plutonium in the blood and their correlation with urinary excretion. Anemia and gastrointestinal problems reduced plutonium excretion by one-half in urine and feces respectively, but half-times were not changed. The exponential notation predicted somewhat greater excretion than the power functions. The model developed predicted equal amounts of plutonium in bone and liver fifteen years after exposure, assuming adequate dietary intake of iron.

A comparison involving both species and mode of representation is shown in table 16.5A, and a comparison of long-term plutonium excretion predicted from sums of exponentials versus power functions is shown in table 16.5B.

TABLE 16.5A. Early Distribution of Pu in Man, Dog, and Pig

		Injected Pu (%)			
	Time After Injection	Skeleton	Liver	Soft Tissue Remainder	Excreted
<i>Man</i>					
This paper	5 to 17 days(a)	47.5	26.8	23.3	2.4
	5 to 15 months(b)	47.5	31.2	11.2	9.5
Langham et al.	4 to 457 days(c)	65.7	22.5	6.8	5.0
Dog(d)	22 days	51.0	34.0	2.0	13.0
Pig(e)	30 days	72.0	14.0	8.3	5.7

(a) Average of Cal-1, Chi-2, HP-11, Cal-3. Livers and skeletons of Chi-2 and HP-11 not included. See Tables I and II.

(b) Averages of HP-5, HP-9, and Chi-1. See Tables I and II.

(c) Average of all tissues from all cases in Langham et al. Excretion estimated from power functions. Soft tissues calculated by difference.

(d) Stover et al.

(e) Skeleton from Clarke et al. Liver from Smith et al. Excreta calculated from exponential equations in Table VI. Soft tissue calculated by difference.

Source: Reset from Durbin 1972, p. 512. For references and tables, see original publication. Reprinted with permission of The J. W. Press, University of Utah, Salt Lake City, Utah, copyright 1972. Note: The symbols for the patients are explained in chapter 7.

TABLE 16.5B. Comparison of Long-Term Pu Excretion Predicted from Power Functions or Sums of Exponentials. [Total excretion as percent of dose.]

Time After Injection		Power Functions, Langham et al.	Sums of Exponentials, This Paper
(days)	(years)		
10		2.56	4.39
20		3.17	5.25
40		3.81	5.95
60		4.21	6.35
80		4.50	6.67
100		4.74	6.96
140		5.10	7.39
360	1	6.26	8.79
720	2	7.22	10.23
1,100	3	7.83	11.17
1,500	4	8.30	12.24
1,800	5	8.68	13.00
3,650	10	9.96	15.47
7,200	20	12.17	18.83
14,600	40		22.49

Source: Reset from Durbin 1972, p. 510. See chapter 7 for Langham et al. reference. Reprinted with permission of The J. W. Press, University of Utah, Salt Lake City, Utah, copyright 1972.

The authors explain that it took three different power functions to describe the data depending upon the time interval. However, for our purposes, the original Langham model (see chapter 7) for daily urinary (Y_U) and fecal (Y_f) excretion rates will be quoted. This is:

$$\begin{aligned} Y_U &= 0.2t^{-0.74} && \text{in per cent per day} \\ Y_f &= 0.63t^{-1.09} && \text{in per cent per day} \end{aligned}$$

where t is in days and is >1 .

Durbin (1972) developed the multicomponent exponential equation as follows:

$$Y_U = \sum_{i=1}^5 a_i \exp(-0.693t/(t_{1/2})_i),$$

where the values of the intercepts, a_i , are 0.41, 0.12, 0.013, 0.003, and 0.0021% dose/day, and the values of the biological half-lives, $(t_{1/2})_i$, are 1.2, 5.5, 42, 300, and 4,000 days, for components 1 to 5 respectively, and

$$Y_f = \sum_{i=1}^5 b_i \exp(-0.693t/(t_{1/2})_i),$$

where the values of the intercepts, b_i , are 0.60, 0.16, 0.012, 0.002 and 0.0012% dose/day, and the values of the biological half-lives, $(t_{1/2})_i$, are 2.0, 6.6, 56, 380, and 4,000 days, for components 1 to 5, respectively.

This is now known in the literature as "The Durbin Equation." It is obvious from table 16.5A that there can be almost as much variation introduced by different models applied to a given species as there is among species. Also, the

sums of exponentials (table 16.5B) predict more excretion by a small but significant amount than the power function. Durbin does not commit herself to favoring one over the other model as "validated" by the reworking of the data. She does emphasize that the rework indicates progressively more plutonium (relatively) in liver over a fifty-year working lifetime. On balance, the conclusions are that some fine-tuning is needed but nothing drastic.

In 1971, Dr. Durbin spent considerable time at Rochester combing the original patient records.^(a) Presumably, she did the same thing at the other institutions. This not only fed data into her reviews, but sowed the seed for possible remeasurement of excreta and in-vivo counting of the survivors. The program of following up radium workers and patients had been very successful (see chapter 1). Could not the AEC (or ERDA) put such a task in place for plutonium, e.g., in the Center for Human Radiobiology at ANL or the Transuranium Registry, discussed later?

The possible political consequences of such a move troubled the AEC headquarters staff (see chapter 7). An ad hoc committee was convened in May 1974 (DBER 1974) to recommend on the scientific merit of studying not only the few individuals still alive, but of mounting an exhumation program similar to that current for radium patients. The committee consisted of Eugene P. Cronkite, Marvin Goldman, Roy Talmage, and Betsy Stover (chairperson). They concluded that the importance of nailing down the figures from these eighteen patients warranted such a program, provided all or nearly all could be done. A program did get started at the Center for Human Radiobiology, but it was kept at a low profile. Two or three exhumations have occurred, and the cremation ashes of one patient were made available for measurement (Rundo 1983). No data have been published yet so far as this author knows. Permission for exhumation was denied in several instances.

As a result of Dr. Durbin's efforts and the interest of all concerned, it was possible in 1973 to hospitalize three of the patients for formal study of plutonium excretion and in-vivo plutonium measurements. Two were placed on the metabolic ward at Strong Memorial Hospital in Rochester and measured by John Rundo from Argonne in collaboration with local staff. The third was hospitalized at the Argonne facility. The results are given in an important paper by Rundo (1981) at the Snowbird Actinide Workshop.

The case that received the plutonium intramuscularly was not followed through because the size of the initial dose was in question. The original dose was given in a leg, which was amputated four days later because of preexisting cancer. (See Case Cal-3 in Durbin 1972).

Two of the HP cases (see table 7.1) were studied completely. Details are given in table 16.6A, taken from the Rundo (1981) paper.

It turned out that the excretion of plutonium at these long times after injection (10,000 days) was very significantly higher than predicted by either the Langham or Durbin models. The retention model for plutonium developed by

(a) It was this author's privilege to help make the arrangements for this, including interviews with the physician attending the patients still alive and in the Rochester area. There were high hopes that some of the original tissue blocks, especially for bone, could be obtained and sections made for analysis of plutonium by modern methods. Unfortunately, the Pathology Archives had discarded those tissue blocks a few months before!

TABLE 16.6A. Details of the Subjects [Restudied] and of the [Plutonium] Injections

Case Number	40-009	40-012
Literature case no.(a)	Hp-3	Hp-6
Sex	F	M
Age in 1973	77	72
Details of injection		
Date	Nov. 27, 1945	Feb. 1, 1946
Material	²³⁹ Pu(IV) citrate	²³⁹ Pu(IV) citrate
μCi	0.301	0.331
Route	I.V.	I.V.

(a) See chapter 7.

Source: Modified slightly from Rundo 1981. Reprinted with permission of RD Press, University of Utah, Salt Lake City, Utah, copyright 1981.

ICRP in Publication 19 (ICRP 1972)(a) was in good agreement at the later times, but not at earlier times. The data are shown in table 16.6B. In one subject, the rate of excretion began to increase at about 6,000 days, reached a maximum at 9,500 days, and declined from that point on (Rundo 1981).

TABLE 16.6B. Daily Excretion at 10⁴ Days as Percentages of Injected Dose

	Urine	Feces	Total
Subject 40-009	2.52×10^{-3}	1.05×10^{-3}	3.58×10^{-3}
Subject 40-012	1.41×10^{-3}	0.53×10^{-3}	1.95×10^{-3}
Langham(a)	2.19×10^{-4}	0.28×10^{-4}	2.47×10^{-4}
Durbin(a)	2.12×10^{-4}	2.12×10^{-4}	4.24×10^{-4}
ICRP 19 (ICRP 1972)	—	—	2.04×10^{-3}

(a) See chapter 7 and text of this chapter for references.

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This increase in excretion at long times was not totally unexpected. Some of the workers of long standing from the MED group showed tendencies for overestimation of the body burden when the Langham equation was used (Rundo 1981). As seen in table 16.5B, the daily excretions of plutonium by these two subjects at 104 days was at least an order of magnitude higher than predicted by

(a) Details of this equation are given by Rundo (1981) and are in ICRP 30 (1979).

the models in current use. Does this invalidate the models? It does not. The models were developed from data to a maximum of five years. The re-examination of the data in no way seriously invalidated either model for times less than five years. Also, the ICRP model, which works well at very long times, "grossly underestimates the excretion rate at early times, overestimates it by a factor of more than 2 at around 1,500 days, and yet is approximately correct at 104 days" (Rundo 1981, p. 258).

The only caution is not to rely on the original models without changes of constants for very long times. Rundo points out the Langham equation provides a good description of the urinary excretion rate up to fifteen hundred days for both of the HP subjects and that Durbin's equation is about equally good after ten days. He gives graphs for each case and for a long-term Los Alamos worker.

It should be noted that the change away from the kinetics of the model means that plutonium body burden at later times would be *overestimated* if the older models were used. Thus, any errors that might have been introduced by use of the equations for long periods of retention would have been on the side of safety. Note, too, that the urinary excretion rates at these times are so small that even a factor of ten is not very much plutonium.

We will hope that additional information on tissue content will be made available from this all-important group of patients. This would put the capstone on this facet of the validation process. Permission for exhumation was denied in several instances.

The Center for Human Radiobiology did contribute later via a joint paper by Bob Rowland, director of the center, and Patricia Durbin (Rowland and Durbin 1976). This involved computation of the probable radiation doses to liver and bone of all eighteen patients and correlation with the effects noted in the radium cases at comparable doses. They concluded that the dose to liver was probably not high enough (in terms of the then-extant ideas about the radio-sensitivity of liver) to be carcinogenic. Comparison of the bone-surface doses for plutonium, with radium doses that had induced bone tumors, indicated that six of the cases had received doses high enough to be regarded as carcinogenic. Neither bone nor liver tumors had yet appeared in any of the cases (nor have they to date [1987]). Thus, to a small degree, this operation, intended to check out metabolism, allowed a small foray into validation of the effects portion of the standard.

2. The Twenty-Five Los Alamos MED Workers

Let us give the setting by quoting the introduction from the first major report on the subject produced at Los Alamos:

This is the story of how 25 young men were heavily exposed to plutonium at what is now the Los Alamos Scientific Laboratory (at Los Alamos, New Mexico) in the days of the Manhattan Project during World War II and of what has happened to them in the subsequent 27 years. All but a few of the subjects of this study were college science majors who were drafted into the Army and assigned to a Special Engineering Detachment of the Manhattan Project. All were sent to Los Alamos (Project Y) in 1944 or 1945 and given various technical jobs in the Chemistry and Metallurgy Research Division. In these capacities, they were engaged in processing plutonium prior to fabrication and testing of the first atomic bomb. Almost all of these subjects had body burdens of plutonium estimated from the urine assay for

plutonium used at Los Alamos before 1950 that ranged from 0.1 to 1.2 μg (0.006 to 0.08 μCi). (Hempelmann, Richmond, and Voelz 1973)^(a)

Recall that the maximum permissible body burden of plutonium was 0.04 μCi . Therefore, some of this population were definitely "over the line." They were selected for the study since they represented a population of great interest to validation of the standard.

This enterprise is a living memory to Wright H. Langham who was "Mr. Plutonium" in biomedical circles throughout the world. Again, we can catch the flavor best by quoting from the first report:

This report of the health of war-time Los Alamos plutonium workers was inspired by Wright H. Langham and is dedicated to his memory. Wright's keen interest in plutonium is known to everyone and, as one of the if not the world's authority on plutonium biochemistry and toxicity, he was the first to be called upon by our government as well as those of other countries whenever plutonium problems arose. His ultimate concern, of course, was the toxicity of plutonium in man and, in this connection, he organized the UPPU Club composed of the subjects of this study. He kept in close touch with the Club members by periodic circulation of friendly UPPU Newsletters. It was undoubtedly the humor and enthusiasm expressed in these Newsletters that has been responsible for the excellent cooperation of the UPPU Club members in this study.

Wright's intense interest in plutonium continued until his untimely death. In fact, an early draft of this manuscript and a number of now declassified war-time reports on plutonium experiences were with him at the time of the fatal plane crash. Although Wright died before he could write his interpretation of the present data, he contributed enormously to the report in the course of discussions of the subject during the winter of 1971-1972. Although we are well aware that the study suffers greatly by not having Wright's direct participation, the authors have tried to write a report of which he would have been proud. In an effort to make the report into a personal living story, which it was to Wright, we have included many of the anecdotes that Wright loved to tell.

(Hempelmann, Richmond, and Voelz 1973, Preface)

Since the whole thing began around body burdens estimated from urinary excretion, the acronym for the club, "UPPU," becomes obvious.^(b)

This study was not primarily to validate the metabolic model. However, since the measurements were made, comparisons to older computations are given. It was to validate the safety of the standard in terms of effects that the work was undertaken. The first full report covered twenty-seven years. Its abstract is reproduced as follows:

(a) Hempelmann, the senior author on this first report, was for many years professor of experimental radiology at the University of Rochester School of Medicine and Dentistry. (We saw some of his earlier work in chapter 1.) However, he was the physician in charge at Los Alamos during the war years and has close ties to these workers and their health. He consistently revisited Los Alamos to keep up with the work. He and his colleagues also published a paper in the *Proceedings of the Third IRPA Congress* on the biomedical follow-up of these workers, a more abbreviated version of the Los Alamos report (Hempelmann et al. 1974). In his present status as professor emeritus, he still maintains contact with this important study.

(b) It was this author's privilege to visit Los Alamos when the club was back for a five-year check-up. No winning sports team or college reunion gathering could have had more spirit.

Twenty-five male subjects who worked with plutonium during World War II under extraordinarily crude working conditions have been followed medically for a period of 27 years. Within the past year, 21 of these men have been examined at the Los Alamos Scientific Laboratory, and 3 more will be studied in 1973. In addition to physical examinations and laboratory studies (complete blood count, blood chemistry profile, and urinalysis), roentgenograms were taken of the chest, pelvis, knee, and teeth. The chromosomes of lymphocytes cultured from the peripheral blood and cells exfoliated from the pulmonary tract were also studied. Urine specimens assayed for plutonium gave a calculated current body burden (excluding the lungs) ranging from 0.005 to 0.42 μCi , and low-energy radiation emitted by internally deposited transuranic elements in the chest disclosed lung burdens probably of less than approximately 0.01 μCi . To date, none of the medical findings in the group can be attributed definitely to internally deposited plutonium. The bronchial cells of several of the subjects showed moderate to marked metaplastic change, but the significance of these changes is not clear. Diseases and physical changes characteristic of a male population entering its sixth decade were observed. Because of the small body burdens on the order of the maximum permissible level in these men so heavily exposed to plutonium compounds, we conclude that the body has protective mechanisms which are effective in discriminating against these materials following some types of occupational exposures. This is presumably explained by the insolubility of many of its compounds. Plutonium is more toxic than radium if deposited in certain body tissues, especially bone; however, from the practical point of view, plutonium seems to be less hazardous to handle. (Hempelmann, Richmond, and Voelz 1973, abstract)

The report contains pictures of the original wooden "D" building, which housed the chemists and metallurgists (see figure 8.13B). Quite obvious are the hood exhausts from the first floor venting without filtration at roof level or below. It is related that the air intake from the hoods went through an electrostatic precipitator, but it is obvious that the chances are high of receiving someone else's exhaust without entry via the hood intake. It seems likely that the bulk of these exposures were by inhalation, although ingestion may have occurred also.

By 1972, a computer code called PUQFUA^(a) had taken over the calculations. The analytical methods were greatly improved, along with the updating of the computational model. The report cites 1953, 1957, and 1962 estimates of body burden and compares them with the 1972 estimate. Almost all of the 1972 figures were higher. The average for the twenty-five subjects was 1.6 times the earlier Langham estimate. Some were higher by as much as a factor of five or six. Only two of the estimates were lower in 1972 than earlier. As a result, eighteen of the twenty-five workers now checked out above the maximum permissible amount at some time, whereas only twelve were in that category in the earlier documents (cited in the report).

The associated radiation doses (calculated) for twelve clear inhalation cases were lowest in bone (5 to 17 rad in about twenty-four years), higher in liver (28 to 95 rad in the same time), and highest in lung (63 to 200 rad). Diligent physical examination and tests showed only the possible changes in lung alluded to in the abstract.

In-vivo measurements of plutonium were possible by this time. The investigators measured plutonium in the chest cavity and searched out areas of lymph nodes, ribs, and some miscellaneous tissues.

(a) Plutonium Body Burden (i.e. $q=Q$) From Urine Analysis.

The search for chromosome damage in blood cells was expected to yield positive results. Experience with the uranium miners and animal studies pointed in that direction. However, the chromosome analysis "indicated minimal radiation damage to the lymphocyte series even at a high level of exposure of the patient" (Hempelmann, Richmond, and Voelz 1973, p. 18).

Sputum cytology work similar to that applied to the uranium miners to detect incipient or actual lung cancer was inconclusive. There were problems with the role of tobacco smoking and the collection of standardized sputum samples.

The report ends without drawing firm conclusions. More time was said to be needed. Obviously, the apparent lack of overt biological effects could be regarded as validating the standard. The higher body burdens calculated from urine analysis are not compared to the in-vivo counting, presumably because there were no earlier in-vivo counts. The phenomenon seems to have been relegated by the authors to the changes in calculation code and perhaps better analytical chemistry.

A five-year update of these workers was contained in a report by the Los Alamos people in 1978. Since this involved other populations and there was nothing new to report in the twenty-six workers,^(a) we will postpone consideration of it until later.

The next full-dress report, this time published in *Health Physics*, was issued in 1979 (Voelz et al. 1979a). By this time, two of the individuals had died, one of a myocardial infarction, the other accidentally. The other twenty-four were examined and measured; twenty-two of them by return to Los Alamos.

The PUQFUA program was adjusted in the interval on the basis of the results of autopsy samples (see next section) and also to better accommodate statistical fluctuations in the samples. The 1977 figures (published in 1978) were lower on the average than the 1972 values and more like the earlier ones. The average calculated body burden was about 60% of the 1972 value.

In the occupational histories, which were given, it is noted that some of the subjects worked with other radionuclides in addition to plutonium. Any such exposures appear to have been low enough to remove fear that insults from additional radioactivity complicated the findings.

The medical histories, given in detail in the published paper, were again devoid of evidence of radiogenic cancers or other dyscrasias possibly associated with plutonium exposure. Only two cancers of any kind were found, and these, cancers of the skin, were attributed to other causes by the Los Alamos group.

The mortality experience in the group was about one-half that expected in white males in the United States. This may reflect the relatively high socioeconomic status of the workers or only the fact that the group is too small to generate reliable mortality statistics.

The latest five-year re-examination had been completed but not yet published at the time this chapter was completed. George Voelz gave much of the information as part of the Health Physics Society's Mid-Year Topical Symposium on Radiation Epidemiology in January 1983.^(b) This report involved a total of 224 persons (Voelz et al. 1983). Informally it appears that the health status of the group is consistent with or better than their age group in general.

(a) In both this and the 1978 report, the occupational MED group is given as twenty-six rather than twenty-five. The identity of the added person is probably hidden somewhere in the in-house reports.

(b) Voelz gave both a formal paper and a "refresher course" of several hours' duration.

The net result of this enormous task is validation of the plutonium standard in terms of effects, except for problems of the small size of the group.

Hail to the Spirit of the UPPU Club!

3. Other Los Alamos Workers

It was obvious that the small group of MED workers could not supply the extensive information on late health effects needed for a proper epidemiologic study. In 1974, the Los Alamos group expanded the study to include all Los Alamos workers, current and past, with body burdens of plutonium of 10 nCi (0.01 μ Ci) or more. The review concentrated on mortality statistics and cancer incidence in the workers. For a control group, the cancer mortality rates between 1950 and 1969, and between 1969 and 1974, among Los Alamos County male residents who lived or worked moderately close to the facility was used.

The first major report was given at an IAEA symposium on late effects of ionizing radiation (Voelz et al. 1978), which was quickly followed by a report at a conference for radiation accident preparedness held in Oak Ridge (Voelz et al. 1979b). The results can be reviewed best by a quotation from the 1978 paper:

A borderline excess of deaths due to the combined cancers of lymphatic and haematopoietic tissues did appear in Los Alamos male residents between 1950 and 1969. Neither mortality rates in females from 1950 to 1969 nor incidence rates in males from 1969 to 1974 were high. This suggests that any excess, if real, was probably occupationally induced prior to employment at Los Alamos or during early years when controls of all hazards, including chemicals, in the work place were not up to current standards. Tumours of lymphatic and haematopoietic tissue differ in aetiology, and it is not suggested that any one factor could be expected to be responsible. Before and during Los Alamos employment some workers could be expected to have been exposed to various hazards of modern technology, including radiation in all its forms and organic and inorganic chemicals.

High incidence rates of cancers of the digestive tract in white males were noted from 1969 to 1974, although mortality from these cancers was significantly low between 1950 and 1969. Digestive cancer mortality rates in females were significantly high from 1950 and 1969, and the incidence rates in females remained above average from 1969 to 1974. No simple explanation is possible, but occupational exposures seem a less likely explanation than socio-economic and cultural factors, counteracted at first by an exaggerated healthy worker effect. Males were selected for active military service originally, and since 1945 for active employment in a demanding industry and for regional geographic mobility. Females were subject to selection in most cases only by marriage to such males. Both sexes could share the same white-ethnic, social or behavioural risk factors, counteracted in the males during the first years by the strong healthy worker, healthy migrant, and/or healthy military effects.

It should be noted that neither mortality nor incidence data suggest an excess of cancer of the lung in the male population of Los Alamos County.
(Voelz et al. 1978, Discussion section)

This expanded study of Los Alamos workers and population did not invalidate the standards. However, even this larger group was considered too small for conclusive results until further information is gathered. A still wider ranging study was desired. This will be discussed presently.

4. Other Worker Populations

As stated at the outset, efforts at validation involved two quite different phenomena—the metabolic parameters and the metabolic models and the

health status of individuals exposed to plutonium. The former involved development of formal autopsy programs and will be discussed as part of the Transuranium Registry. The latter is an ambitious effort to follow up all plutonium workers at Hanford, Los Alamos, Mound Laboratory (Miamisburg, Ohio), Oak Ridge, and Savannah River. With unexposed controls, this population could number about twenty thousand, but only a small number will have measurable body burdens of transuranic elements.

It should be noted that studies of *population* exposures around nuclear energy installations such as Rocky Flats were discussed in chapter 11. In a sense, these can be regarded as potential validation procedures for population exposure standards. However, since they were not designed for this purpose, and the results are still too qualitative to serve for validation, we will let the discussion in chapter 11 suffice.

5. Autopsy Programs for Plutonium and the Transuranics

a. Independent Programs

As early as 1949, a small program of tissue sampling was started at Hanford. The object was radiochemical analysis for ^{239}Pu , for comparison with amounts calculated from excretion measurements. Bone, liver, and lung were routinely analyzed, and, in 1960, collection of pulmonary lymph nodes was added since most of the exposures were judged to be by inhalation.^(a)

This work was reported in depth by Newton et al. (1968) at a Hanford symposium. The conclusions were, unequivocally, that the predominant source of plutonium contamination was not from occupational sources, but from fallout from nuclear weapons testing. The measured and predicted tissue contents squared very nicely using the predictions of the fallout model. Thus, the work validated the fallout model insofar as any model can be relied upon.

It is interesting to note that one of the highest concentrations (130×10^{-3} d/m/g; not really very much) occurred in the lymph nodes of a worker with ten years of work exposure.^(b) This is reminiscent of the autopsy findings on one of the workers involved in the Los Alamos criticality accident (Mr. Kelly). He had had considerable work exposure to plutonium. The animal work (chapter 9) was showing very high concentrations in the lymph nodes. So did his.

Another point of interest was the fact that liver depositions were greater than lung in many instances. Unfortunately, the data for bone were inconclusive.

During the autopsy program at Los Alamos, concentrations in gonad (especially testis) were found to be higher than expected. Indeed, with the high relative biological effectiveness of alpha emitters, the calculated doses in rem over long periods elicited concern. It turned out that some of the early results on very small samples were in error. Harry Schulte, the group leader of Industrial Hygiene at Los Alamos, sent a memorandum to recipients of the early version of the report (Schulte 1973) stating that the data on larger samples of gonadal

(a) A program aimed more at fallout levels of contamination was reported by Krey, Bogen, and French (1962). They were impressed by the high percentages of the maximum permissible population dose delivered to lungs, pulmonary lymph nodes, and gonads by the fallout plutonium found in autopsy tissues. This program does not seem to have been extended.

(b) The late start on measuring lymph nodes resulted in many blank spaces under that heading.

tissues were practically all below the minimum detectable level. Nevertheless, concern for genetic effects of plutonium persisted until experimental work, quoted earlier, indicated no special sensitivity toward deposited radionuclides for mutations in the mouse, at least.

b. The U.S. Transuranium Registry

At a Hanford Biology symposium in 1967, H. D. Bruner from AEC Headquarters (whose work we met in chapters 8 and 9) presented a paper entitled "A Plutonium Registry" (Bruner 1968). He pointed out that full information for long-term evaluation of internal contamination requires full input from not only the attending occupational physician, but also from health physicists, industrial hygienists, and chemical engineers. In his view it is expecting too much of the busy industrial medical person to collect and collate all of the necessary information. Furthermore, it is unrealistic to expect the individual physician to write the final clinical reports for such cases. The follow-up period is much too long. In Bruner's view, only a formal organization could respond adequately to the needs. He suggested such an organization for the plutonium cases that then numbered about 330 persons. He also suggested including other transuranic elements fairly soon.

Evidently the same idea had been incubating in the mind of W. D. ("Dag") Norwood, the industrial physician at Hanford. Events moved rapidly with official blessing from AEC Headquarters (i.e., funding), and Dag Norwood became the Registry's founding director. A contract was let with HEHF in Richland, Washington, for a National Plutonium Registry. In 1970, the name was changed to U.S. Transuranium Registry (USTR).

The purposes and *modus operandi* can be gained from the Program Description in a recent annual report of the USTR:

The purposes of the USTR are to study the patterns of distribution, concentration and retention of transuranics in exposed individuals by radiochemical analysis of selected post-mortem tissues; to evaluate the estimates of body or lung burdens made during the life of the individual and compare them with estimates based on the analysis of selected tissues obtained after death; to assess toxic histopathologic changes, if any; to compare findings in animal experiments with estimates in humans who have transuranic depositions; and to serve as a national and international resource center concerning the transuranic elements in man.

An exposed individual is one who has a documented exposure to one or more transuranics, either with or without a measurable deposition. The study population has been composed primarily of occupationally exposed employees of the various Department of Energy (DOE) contractors and Nuclear Regulatory Commission (NRC) licensees. This does not exclude, however, individuals exposed to these elements in research institutions or the uniformed services. The last two resources have not yet been approached on a large-scale basis.

The Registry, working through major DOE contractors and several NRC licensees, identifies employees who have the potential for internal deposition of transuranic elements. These employees are interviewed by contractor medical personnel to verify the potential for internal deposition of transuranic elements. These employees are interviewed by contractor medical personnel to verify the potential exposure and to seek voluntary participation in the Registry at the time of the interview. A medical and health physics release is obtained from those employees who volunteer to participate. Previously terminated employees also have been identified and contacted for participation if they have evidence of a transuranic

deposition. This contact may have been made either by the Registry or by the participating contractor, depending upon prior arrangements.
(HEHF 1983, p. 1)

There have been 647 valid autopsy releases from Hanford, Rocky Flats, Los Alamos, and Mound Laboratory; none to date from Oak Ridge or LLL. A few employees of licensees and three volunteers swelled the total to 825. Of these, 220 have been autopsied, and radiochemical analyses have been completed on 147 cases. This is a major effort at validation.

A few notes on procedure are in order:

At the time of death a post-mortem examination is performed and a complete written pathology report is obtained along with supporting medical information and health physics data. A set of histopathological microscopic slides is obtained for later review. The radiochemical analysis of donor tissues is performed at either the Los Alamos National Laboratory (LANL) or the Rocky Flats site (Rockwell International Company, Golden, Colorado). The laboratories maintain an ongoing quality assurance program involving the comparison of analytical data to ensure comparability and uniformity in the analyses. A library of previously analyzed tissue sample aliquots has been kept so that reanalysis of specimens or analysis for other radioisotopes may be performed.

The Registry has identified special prosecutors to assist with the post-mortem examination and thereby assure uniform selection and preparation of tissues for analysis. These prosecutors are available at major contractor sites.
(HEHF 1983, p. 2)

The autopsy results to date have shown that estimates made by in-vivo counting and excretion measurements tended to be higher than those based on tissue analysis. However, this was considered largely due to analyzing "nonrepresentative" portions of the organ samples obtained. The Registry has been making a strong effort to obtain donations of the whole body rather than the usual small autopsy samples. The amount in total skeleton is especially important to measure because of the known variations in deposition of plutonium and other transuranics in different bones. Permission has now been obtained for twenty-four whole-body examinations upon death, and there have been seven deaths in the group. The first contained so little transuranic radionuclide that total tissue analysis was given up. The other was a case of deposition of ^{241}Am .

Validation of the metabolic model for this man is not discussed very directly in the reports. If the estimate of the in-vivo measurements, $0.3 \mu\text{Ci } ^{241}\text{Am}$ systemic burden with initial depositions of 0.5 to $1.1 \mu\text{Ci}$, is compared to the summed tissue samples, $0.15 \mu\text{Ci}$ with initial deposition of about $0.6 \mu\text{Ci}$, it appears that the conclusions drawn from small tissue samples are being confirmed. The in-vivo estimates seem to be high by a factor of about two. Yet, we find in the 1981-1982 annual report the statement, "Preliminary data from the first whole body tissue analysis indicate that the health physics estimate of systemic burden is comparable to the post-mortem estimate in this case" (HEHF 1983, p. 2). This is the same case; the difference is in point of view. Details appear to need considerable adjustment, and the computer codes are being modified accordingly.

When the hundreds of analyses involved are considered, it could be concluded that losses in the radiochemical procedures could sum up to a factor of two. Also, the computer codes are far from infallible. We must await developments.

The factor of two appeared again very recently in a presentation by McInroy (one of the radiochemical analysts involved in tissue analyses at the DOE Human

Tissue Laboratory at Los Alamos) and colleagues from Los Alamos (McInroy et al. 1982). They report on tissues from 180 autopsy cases from various facilities. The plutonium levels were, in general, those associated with fallout. For the twenty cases with the highest depositions (maximum 0.05 μCi), the urinalysis data gave estimates "that are high by factors of 2-3, or more." The authors note the considerable variability in whole-body distributions and suggest that each exposure incident is unique and must be evaluated on the basis of chemical form, solubility, particle size, mode of entry, and duration of exposure. Incidentally, some of the cases were in the Transuranium Registry.^(a) The others were from the Los Alamos series, which began well before the USTR was organized. It must be emphasized that the USTR is not an epidemiologic study. It does not engage in measuring mortality rates for any specific diseases; this is left for others. The analyses do, however, include careful and complete histopathologic examinations.

The personnel serving the Transuranium Registry and management are listed below:

United States Transuranium Registry Management

Bryce D. Breitenstein, Jr., M.D., President,
 Hanford Environmental Health Foundation (HEHF)
 Scott E. Dietert, M.D., Manager, Research, HEHF
 Margery J. Swint, M.D., Director
 Ronald L. Kathren, Consultant, Battelle, Pacific Northwest Laboratories
 (now full-time with HEHF)
 Patricia Blackburn, C.P.S., Secretary

Prosectors

Robert W. Bistline, Ph.D., Rocky Flats Plant
 Gerald Dagle, D.V.M., Ph.D., Battelle, Pacific Northwest Laboratories
 James McInroy, Ph.D., Los Alamos National Laboratory
 E. J. Reagan, M.D., Mound Laboratory
 William H. Carlton, Savannah River Plant

Advisory Committee

J. W. Poston, Ph.D., Chairman, College Station, Texas
 R. D. Evans, Ph.D., Vice Chairman, Scottsdale, Arizona (resigned 1986)
 P. W. Durbin, Ph.D., Chairman, Technical Advisory Committee, Berkeley, California
 C. W. Mays, Ph.D., Salt Lake City, Utah
 J. Newell Stannard, Ph.D., San Diego, California
 Langan W. Swent, San Francisco, California
 George Voltz, Los Alamos

The Advisory Committee serves also for the Uranium Registry, which will be discussed presently. For many years, Bryce D. Breitenstein, Jr., M.D., was director, and Kenneth R. Heid was associate director of the Transuranium Registry (HEHF 1983). There have been a few changes since (HEHF 1985).

6. Mancuso Study

An ambitious epidemiologic study of selected radiation workers was initiated in 1964 by the AEC and continued by its successor agencies. It was spearheaded until 1977 by Dr. Thomas Mancuso at the University of Pittsburgh. Mortality

(a) Note added in proof: Further details can be seen in a symposium paper published by Heid in 1983 and the annual reports of the Registry.

from all causes was determined for workers principally at Hanford and at Oak Ridge. Since the Hanford group included plutonium workers, it could be imagined that this study might have a bearing on validation of the plutonium standard. It did not, because the measures of radiation dose were from film badges, thermoluminescent dosimeters, etc., and thus were confined to external radiation sources. Indeed, it is difficult to ascertain whether or not the possibility of an internal dose was factored into the study even though its presence could influence the results. In some reports it appears that it was, in others that it was not.

We should probably drop the subject here. However, the results have been quite controversial and we feel duty-bound to help the reader find more. Mancuso stormed off the project with charges of bias and suppression of information by the sponsors. Others joined the fray, and much of the potential benefit of an objective analysis became difficult to achieve. Samples of the publications with special bearing on Hanford are as follows: Mancuso, Stewart, and Kneale 1977; Gilbert and Marks 1979a,b; Kneale, Stewart, and Mancuso 1979a,b; Gofman 1979; Tait 1979; Hutchinson et al. 1979; Kneale 1981; Kneale, Mancuso, and Stewart 1981; Spiegler 1981; Gofman 1981b; Tolley et al. 1983; Kneale, Mancuso, and Stewart 1984; Gilbert and Petersen 1985. Of these, the Gilbert and Marks paper in *Radiation Research* is a full presentation that refers to earlier full treatises. Many of the others are exchanges of letters. Gofman gives detail, including an analysis of his own in his book (1981a).

7. Validated?

On balance, the enormous efforts detailed above can be said to prove that there are no terrible mistakes in either the metabolic models or the basic standards for plutonium based on effects or projected effects. A factor of two, even somewhat more, must be considered within experimental error in so complex an enterprise. Furthermore, the work points strongly to handling each case as a separate entity.

The USTR has served well so far in validating the basic features of the models. But it has turned up many differences in detail. These have been (and are being) used to modify the models via the computer codes.^(a)

In chapter 9, we reviewed the "Hot Particle" problem as applied to depositions of plutonium in lungs. There is little possibility that the standards could be high by the enormous factors postulated therein. The validation process described above would have surely revealed a mistake of this magnitude. Yet, as detailed in chapter 9, we are still not sure about the significant area (or volume) and therefore the significant dose to lung. (See also Stannard 1975, where the effect of changes in metabolic models, critical tissue, critical tissue weight or volume, etc. on derived levels for ^{238}Pu and ^{239}Pu are described.)

Morgan (1975) proposed a reduction in permissible exposure to plutonium and other transuranic elements by a factor of two hundred. This was derived by a series of factors for (1) increase of the n factor from five to fifteen on the basis of the Utah dog work, (2) difference in the surface-to-volume ratio of bone in man compared to dog, (3) difference in rate of turnover of radionuclides in bone of dog compared to man, (4) relative sensitivity of baboon versus dog, and (5) a general feeling that the linear hypothesis for dose-response relationships

(a) Ford et al. (Oak Ridge) began the process of modification in 1978.

may not be sufficiently conservative. The validation process described above for plutonium should surely have turned up a factor of two hundred too high. The only reservation is that the group size is still small. Final conclusions hang upon the large study involving over twenty thousand subjects, which will require many years for completion.

Two recent additions to the literature on the actinides contribute further to the subject at hand. The first is an International Conference on the Radiobiology of Radium and the Actinides in Man, published as a supplement to *Health Physics* (Rundo, Failla, and Schlenker 1983). The second is a gathering in a special issue of the same journal of a series of papers on the 1976 americium exposure incident (Thompson 1983). Both of these provide more new information on incidents and research than on the validity of standards, but they are important nevertheless to this review.

B. Validation of Uranium Limits

The story for uranium is quite different from that for plutonium. Even quite early there was evidence of discrepancies between predicted body and organ burdens and the actual; and evidence of marked differences between animals and humans in the chemical toxicity of uranium. Despite these facts and the fact that the uranium worker population was one of the largest in the World War II years and in the decade of the 1950s, the amount of follow-up was pitifully inadequate for several decades. In this section, we will examine the early studies first and then the more recent efforts to catch up before it is too late.

1. Earlier Findings

In chapter 2, we reviewed the work done with patients at Rochester during the war and at Boston, Oak Ridge, and Rochester in the early postwar years. These were in part validations of the older metabolic data for humans and the growing fund of information from animals.^(a) The information from this work was used as much to establish new facts and metabolic constants as for validation of what had been for man a modest collection of data.^(b)

Hundreds of employees of the various companies processing uranium to produce nuclear-grade uranium metal and compounds were exposed to dusts and fumes of the metal. Only a few of the processes were "wet," most were dry and very dusty. With some exceptions that we will note later, industrial hygiene measurements and control in the war years were primitive or absent altogether. In the early postwar years, the New York Operations Office of the AEC undertook systematic industrial hygiene measurements of all uranium processing establishments; concentrating on airborne dust. The lung model of the day (see section VI A) was used to predict lung content, and the then-current metabolic model was used to compute amounts in other tissues. These were based largely on experience in dogs. The story is told in fascinating style by Merrill Eisenbud, who was director for many years of the AEC Health and Safety Laboratory in New York. Tissues from two men who died of nonoccupational causes but who had long histories of exposure to high concentrations of uranium dust yielded

(a) All important references have been cited either in chapter 2 or earlier in this chapter.

(b) Use of the Boston experiment as a therapeutic modality is taken up in chapter 20. See also Hursh and Spoor (1973).

measured amounts startlingly less than predicted (0.35 $\mu\text{g/g}$ measured versus 600 $\mu\text{g/g}$ predicted in lung for one case and 0.23 versus 56 in the other case). This began the process. Case after case came in with the same picture (Eisenbud and Quigley 1956; Eisenbud 1975). The agreement between predicted and observed values was much better for bone.

Urinary excretion was so erratic that little could be done to compare measured and predicted amounts in a given individual. However, the individual differences had much less influence when averages of many individuals were used. In fact, Eisenbud and Quigley note that conclusions regarding the amount of uranium excreted in urine in persons exposed to the (MPC)_a of uranium was in "excellent agreement with the predictions of Neuman based on animal data" (Neuman 1950).

The chief problem for validation of the metabolic models seems to lie in the lung deposition figures. Eisenbud gives a possible explanation. The predicted alveolar deposition was based on particles of unit mass. Uranium dust is so very much heavier that the 2- μm particles assumed to deposit in alveoli probably never got beyond the nasopharynx.

The second discrepancy was in the effects produced. Exposures were very high in some of the World War II plants (Eisenbud 1975). Some were recorded at two hundred times the permissible air level, but this probably included considerable nonrespirable dust. Nevertheless, the chemical toxicity noted in the animal work predicted a rash of kidney problems in these workers. There were cases of albumin and casts in the urine, as we have seen, but little else.

Let us review the situation in the forceful language used by Merrill Eisenbud under the heading, "The Need for Epidemiological Follow-up."

The Manhattan District during World War II was of necessity a highly compartmentalized organization in which investigations were carried on at a frenetic pace and in many cases without the opportunity for the kind of exchange of information that one normally expects in the scientific community. The pharmacological and toxicological properties of uranium were investigated mainly at the University of Rochester under the direction of Dr. Harold Hodge and his very able staff. The studies conducted at Rochester were published in 1949 as part of the National Nuclear Energy Series in four volumes that totalled nearly 2500 pages. In contrast, there were essentially no wartime data on the levels of exposure that existed in the various plants, and there was essentially no medical surveillance of these employees. With the formation of the Atomic Energy Commission, and the New York Operations Office, systematic studies began in late 1947 and continued until the shutdown of the old plants by about 1954.

In 1955, the first United Nations Conference on the Peaceful Uses of Atomic Energy was held in Geneva, and the United States' contribution included two major presentations on the toxicology of uranium. The writer, in association with Joseph Quigley and others of the HASL team, summarized the results of the studies that had been conducted up to that time. With respect to chemical toxicity, the conclusions of this paper were very different from the report from Rochester, which was based on findings in animals:

"There has been sufficient experience with severe exposures to both soluble and insoluble compounds of uranium to permit the conclusion that uranium has a low order of chemical toxicity in man. Many of the nonradioactive heavy metals, such as lead, arsenic, and mercury, would produce very severe, perhaps fatal, injury at the levels of exposures reported here." (from HASL).

"Uranium is one of the most toxic elements chemically, more toxic than arsenic or mercury." (from Rochester).

At the 1958 conference^(a) on the health experience of the uranium industry, Mont Mason stated that there was no demonstrable damage to any employee due to chronic uranium exposure. Considering the high exposures of the past, Mason added: "We are not at all smug about this—only grateful." This was also the conclusion of the HASL group. So far as the chemical toxicity of uranium is concerned, we are fortunate indeed that man is less susceptible than the laboratory animals.

However, this statement could be made with more confidence if there had been more thorough follow-up of those who worked in the early production plants. I was disappointed while preparing this paper to find that there had been so little additional information accumulated since 1955.

(From Eisenbud 1975, pp. 13-14, references deleted.)

Eisenbud concluded his paper with the following: "There is reason to believe, based on the few human data that do exist that the chemical toxicity of uranium (in man) is far less than was anticipated. . . . While this is reassuring, the cases are too few to constitute any more than highly equivocal evidence. The laboratory evidence from the University of Rochester leads one to conclude that uranium is highly toxic. The field studies suggest the contrary. Only epidemiological follow-up of the uranium workers can produce the information we need." (Eisenbud 1975, p. 15)

Eisenbud also notes that the literature on animal toxicity and mechanistic studies approached three thousand or more pages, while the epidemiologic literature for the same period did not exceed twenty-five pages!

Actually there was more stirring toward epidemiology than Eisenbud implies. It happened that Eisenbud's presentation came close to the very beginning of the 1975 conference. Later, there were full sessions with reports aimed at finding effects by representatives from ore processing mills, uranium refineries, a fuel fabrication operation, and the Oak Ridge Gaseous Diffusion Plant. Furthermore, representatives of the NRC and ERDA reported their occupational experiences, and there was a review of cancer mortality in uranium mill workers.^(b) (See also Archer, Wagoner, and Lundin 1973.) It must be admitted that none of these were formal epidemiologic studies, nor was there any sign of coordination among the contractors or in Headquarters to make full use of the information. This, while better than nothing, did not give the impression that the investigators were really trying very hard to follow up. The lack of effects in the early studies seems to have discouraged such an effort.

Asher Finkel, whom we met in chapter 1 when he was associated with the Argonne Radium Project and who had meanwhile assumed responsibility for occupational medicine in the American Medical Association, asked, as part of a panel discussion at the 1975 meeting, "Why isn't there a uranium registry? Why is the transuranic element registry so unwilling to take on uranium as an additional project?" (ERDA 1975, p. 352)^(c)

Some steps toward epidemiology were described at the 1975 conference. A study had been undertaken in 1962 by a group at the University of Colorado to determine the *feasibility* of conducting an epidemiologic investigation of the health of workers in a few typical uranium feed plants. This was headed by Dr. Robert F. Bell and has been identified as "The Bell Study." There were four

(a) A meeting on uranium in New York reviewed in USAEC Report HASL-58.

(b) The full program for this conference is shown as note 5 at the end of this chapter.

(c) The author of this book asked the same question at an advisory committee meeting of the USTR somewhat earlier. The answer was that funds were not available.

unpublished documents between 1962 and 1966 and a supplementary commentary by Joseph Quigley of National Lead Company in 1967. The conclusions were that the information desired *could* be obtained, i.e., such a study was feasible. Dr. Quigley even recommended that a full-scale study be undertaken. This development was reviewed by Sidney Marks, then at ERDA Headquarters, at the 1975 conference (Marks 1975). Subsequent to the Bell Study, it was decided to include the uranium feed plants in the ERDA Health and Mortality Study conducted by Dr. Thomas Mancuso at the University of Pittsburgh.

The overall cancer rate for the plant studied most thoroughly was not significantly different from that in the community. Why do they not talk about kidney damage? The fact is that little evidence was found for it. Why?

Remember from chapter 2 and the Hursh-Spoor reviews cited earlier in this chapter that the chemical toxicity of uranium seen in the animal experiments is very dependent on the dosage regime. Tolerance can develop quickly and significantly when a series of small doses precedes a larger dose. There is reason to believe this occurs in man also. Therefore, the lack of evidence for kidney damage in the long-term plant experience may rest upon the phenomena of tolerance. Obviously, the difference between humans and animals may represent more than this, but it is a factor that must be considered in any serious epidemiologic study.

The animal experiments of the 1950s and 1960s were, of course, essential to the building of the models in the first place.

2. Other Developments in the 1970s

Undoubtedly, one reason for the lack of interest in validation work for uranium was the marked decrease in processing of uranium. With the development of plans for new fuel cycles in the early 1970s, including a possible uranium-thorium cycle, interest appears to have been heightened. The Energy Research and Development Administration produced a bibliography on Occupational Health Aspects of Uranium, citing one hundred references in the period 1971 to 1974.^(a) Many of the cited references concern urinalysis, bioassay, in-vivo measurements in lung, tissue contents, and basic biochemical behavior. About half are from countries other than the United States. However, there is, as Eisenbud stated, little epidemiology. One paper, from Oak Ridge, discussed mortality experience of uranium compared to nonuranium workers (Scott et al. 1972), and another by Archer and colleagues (1973) considered cancer mortality in uranium mill workers. Although it was not a full-fledged epidemiologic study, the results were interesting. The mortality experience was more favorable for the uranium workers than for the nonuranium workers in the same plant.^(b)

An important development of the early 1970s pertinent to validation of the uranium figures came from the U.K. Atomic Energy Authority. Donoghue et al. (1972) analyzed tissues from a uranium worker of ten-years' standing who died suddenly from natural causes. Quite complete airborne dust and urine sampling had been carried out. The concentrations ($\mu\text{g U/g wet tissue}$) were 1.2, 1.8, 0.09, and 0.14 for lungs, lymph nodes, sternum, and kidneys, respectively. These amounts are less than 1% of the amounts calculated from the environmental

(a) This was called "preliminary," but I have not found a later version.

(b) Note this was *not* during the period of "dirty" operations.

data! In agreement with the ideas expressed by Eisenbud regarding deposition of uranium dust, a large proportion of the inhaled dust was deposited in the nasopharynx.

The authors suggest possible explanations for the low deposition: (1) pulmonary clearance processes for insoluble uranium dust may be very much faster than the ICRP's 360-day half-life would predict, or (2) deposition is indeed much smaller than the models predict. They favor the second alternative because of the quite small amounts found in urine, again far below the model predictions.

Donoghue et al. give a fairly complete history of work prior to about 1971 on the pharmacokinetics of uranium in the human respiratory tract. Their table is reproduced below as table 16.7A, which gives also some of the results. In table 16.7B, amounts of uranium in lung, kidney, bone, and liver of exposed and unexposed human subjects are given. The important conference sponsored by ERDA on uranium problems has already been cited (ERDA 1975, Hursh 1975).

TABLE 16.7A. Human Metabolism of Insoluble Uranium

Investigator	Place	No. of Exposed Persons	Chest Burden		Biological Half-Life (days)	Substance
			mg	nCi		
Miller (1957, 1958) McLendon (1959) Fish (1961) Fish and Patterson (1958)	Oak Ridge	1	3	30 ⁽¹⁾	21 and 121 (two mechanisms)	U ₃ O ₈ (enriched)
Scott and West (1964) West and Scott (1969)	Oak Ridge	4	0.5-2.0	20-50	Range 550-1500	Uranium oxide, ceramic, or alloy ⁽²⁾ (enriched)
Saxby et al. (1964)	Aldermaston Harwell	2	1 ⁽¹⁾	60	11 and 360 (two mechanisms)	Uranium oxide or silicate ⁽²⁾ (enriched)
Schultz (1966)	Oak Ridge	4	0.01-1.0	1.0-30	Range 120-250	U ₃ O ₈ (enriched)
Ronen (1969)	Negev	1	207	140	100 and 1200 (two mechanisms)	Uranium oxides and (probably) other uranium compounds (natural)
Quastel et al. (1970)	Ottawa	15	10-100	6-60	No information	UO ₂ (natural)

⁽¹⁾Estimated value.

⁽²⁾Probably U₃O₈.

Source: Reset from Donoghue et al. 1972. Reprinted with permission of the British Journal of Industrial Medicine, London, England, copyright 1972. Most of the "investigator" references have been cited in this book (see author index).

TABLE 16.7B. Deposited Uranium in Unexposed and Exposed Human Subjects

Investigator	Year	Exposure	Concentration of Uranium ($\mu\text{g U/g wet tissue}$)			
			Lung	Kidney	Bone	Liver
Quigley et al. ⁽¹⁾	1958	None	0.089	0.026	0.028	0.093
Quigley et al. ⁽¹⁾	1958	None	0.006	0.020	0.004	0.008
Butterworth	1958	None	0.05	—	—	0.02
Lynch	1966	None	—	0.03	—	—
Hamilton	1969	None	—	—	0.004	—
Butterworth	1958	Soluble	0.15	0.08	—	—
Butterworth	1958	Insoluble	0.05 ⁽²⁾	0.06	—	—
Quigley et al. ⁽²⁾	1958	Insoluble	1.02	0.038	0.048	—
Meichen	1962	Unknown	1.6	0.12	—	0.04
Donoghue et al.	1970	Insoluble	1.2	0.14	0.09	0.02

⁽¹⁾Quigley stressed the advisability of analyzing fresh postmortem tissue which has not been placed in a chemical preservative. Some of his data, however, were obtained from preserved tissues and on this account may be less reliable.

⁽²⁾The concentration of uranium in the associated lymph nodes was 0.12 $\mu\text{g/g}$ wet tissue.

Source: Modified slightly and reset from Donoghue et al. 1972. Reprinted with permission of the British Journal of Industrial Medicine, London, England, copyright 1972. Note: The original references for this table are not given here. Most, except Meichen, have appeared in this book (see author index).

3. The U.S. Uranium Registry

In 1978, at long last, a U.S. Uranium Registry (USUR) was organized by ERDA. Funding was provided by ERDA and continued by its successor, DOE; and it was placed under HEHF along with the Transuranium Registry. It was described by Marks at the Snowbird Actinide Symposium (Marks 1981).

The major goals of the Registry were stated as:

1. to characterize the front end of the uranium fuel cycle for electrical power production;
2. to do a feasibility study on establishing a centralized registry of all uranium workers; and
3. to establish a voluntary tissue donation program patterned after the successful USTR.

The inclusion of the entire uranium fuel cycle meant that the uranium miners came under its umbrella. Note also that, while the USUR is primarily an autopsy program like the USTR, there is a potential for identification of populations for epidemiologic study, presumably to be done by someone else.

The staff and management are shared with the USTR, but there is a separate director, Dr. Robert H. Moore, and an identifiable program.

The first report was a field study of the commercial fuel cycle and was published in April 1981. This was primarily to identify processes and sites and to begin the process of getting permission for autopsies, etc. The second report concerned uranium and hard-rock miners.

It is regrettable that the Registry was founded so long after the days of serious overexposures. However, the population is large enough that meaningful results may still be possible. The work is progressing actively.

The personnel for the Uranium Registry are all part time by sharing with the Transuranium Registry (see previous listing) or with other units in the Richland complex, principally PNL.

The personnel most identified with uranium problems (as of 1985) are:

Bryce D. Breitenstein, Jr., M.D., President, HEHF
 Scott E. Dietert, M.D., Manager, Research, HEHF
 Robert H. Moore, M.D., Director, USUR
 Ronald Kathren, consultant, Battelle Pacific Northwest Laboratory
 (now full-time with HEHF)
 Patricia Blackburn, C.P.S., secretary

Note that the Advisory Committee named on page 1471 serves both the Transuranium and the Uranium Registry.

Dr. James McInroy, at Los Alamos, and Dr. Robert W. Bistline, at Rocky Flats, coordinate the bulk of the analytical data for both registries. While they are not officially employed by the registries, their contributions to, and interrelationship with, the enterprise are enormous.

4. The Oak Ridge Epidemiologic Studies

The Medical Division of the Oak Ridge Associated Universities (ORAU) has undertaken a formal study of the World War II uranium worker populations. This was apparently stimulated and guided in its initial stages by Clarence Lushbaugh, a pathologist who spent many years at Los Alamos and who has been much in demand for the many hearings of the past decades. This study considered first a total of about forty-five thousand persons estimated to have worked at the Tennessee Eastman Corporation (TEC), a subsidiary of the Eastman Kodak Company, which operated the Oak Ridge Y-12 plant from June 1943 to May 1947.^(a)

The official reasons given for selecting the TEC group were: (1) long period of follow-up; (2) availability of data in the final year or so on average levels of uranium dust in air, including high levels in some operations; and (3) large sample size.

The first report was a study of mortality prepared by A. P. Polednak and E. L. Frome. It was presented at a DOE statistics symposium at Gatlinburg, Tennessee, in October 1979 and published in 1981 (Polednak and Frome 1981). They used records of the Social Security Administration and standardized mortality ratios (SMR) for various causes of death. The SMR values were generally less than 1.00, i.e., less mortality than in the general population. This was attributed to the "healthy worker" effect. However, after correction for unascertained deaths and missing death certificates, the SMR for lung cancer in the entire cohort was 1.22, with confidence limits (95%) from 1.10 to 1.36. However, neither this nor other SMR values was higher in the more than eight thousand workers who had contact

(a) This author was personally delighted to see that this population had been selected. His implicit faith in the competence, good judgment, and appreciation of future needs by Dr. James Sterner, who was medical director of TEC, made it seem likely that the industrial hygiene would have been better than average for the day and the medical records good enough for retrospective epidemiology, assuming they were preserved.

with uranium compared to others who did not. Leukemia, bone cancer, and respiratory and urogenital tract dyscrasias did not have elevated SMR values.

The air sampling data and methods of the final years are given in detail, including both particle-size distributions and the specific activity of the particles, important since this was an enrichment process. There is also a summary of urinalysis records. However, no comparison is made between predicted urinary uranium and actual.

Some calculations are made of possible radiation dose to the lungs from exposure to 150 μg insoluble natural uranium per cubic meter.^(a) These were 125 rem after one year of exposure, 30 rem after a ten-week exposure, not insignificant.

The elevated lung cancer incidence was confined to "alpha chemistry workers" hired at age forty-five or later. The data are complicated by the presence of chemically toxic substances such as phosgene, solvents, mercury, etc.; by the usual problems of using the diagnosis placed on a death certificate; and the fact that the study is far from complete.

Little mention is made of kidney pathology, kidney function disorders, or diseases of the circulatory system (which might be expected from chronic kidney damage). In fact, the SMR values are considerably less than one for diseases of the genitourinary system and for diseases of the circulatory system. These values were greater than one only for electrical workers (181 cases out of 1,172 workers). Obviously, this study provides an excellent start but no startling surprises.^(b)

The second major contribution from this study zeros in on the lung cancer picture. In a paper delivered at the 1983 Mid-Year Topical Symposium of the Health Physics Society, Diane Cookfair, at the time of the work a doctoral candidate in epidemiology at the University of North Carolina at Chapel Hill (Cookfair et al. 1983),^(c) examined cases and controls from 19,412 TEC employees. There were 330 cases of fatal lung cancer in the cohort between 1943 and July 1973. Age and smoking status were given particular emphasis.

A statistically significant excess in risk for men over age forty-five when first exposed appeared with calculated lung doses of 20 rad or more (200 to 400 rem depending on whether the old or the new Quality Factor is used). The broad results are shown in table 16.8.

There seems little doubt of the age effect. The effect did not seem to be greatly different in the smokers, except for the high-dose (20 to 74 rad)^(d) group, where the odds ratio was 8.62 for cases versus deceased controls and 11.60 for cases versus live controls. The study concludes that older age groups may be more susceptible to radiation-induced lung cancer.

(a) Remember that the permissible air levels were in the range of 200 $\mu\text{g}/\text{m}^3$.

(b) The travail behind the scenes for mounting such a study is seldom appreciated. For many years, a storage room on the roof of the University of Rochester Atomic Energy Project contained rows of old wooden files with cards concerning MED workers. When a third story was put on the building, the card collection was almost thrown out. Fortunately, it was shifted to Oak Ridge, where it was transferred to computer tapes. Clarence Lushbaugh had the task of determining to which operation a given card pertained and gradually assembling the TEC workers. This was presumably added to records already in Oak Ridge. Other populations await study.

(c) Dr. Cookfair is now on the staff of the Roswell Park Memorial Institute, Buffalo, New York.

(d) A separate paper from the Oak Ridge group described the radiation dosimetry for lung (Beck et al. 1983).

TABLE 16.8. Cumulative Lung Dose Odds Ratios from the Stratified Analysis by Level of Exposure and Hire Age, Smokers Only

Level of Exposure*	Cases Vs. Deceased Controls		Cases Vs. Live Controls	
Hire Age <45	OR (95% CI)**		OR (95% CI)	
Low	0.78	(0.35, 1.72)	0.30	(0.15, 0.61)
Medium	0.39	(0.16, 0.96)	0.19	(0.08, 0.43)
High	0.57	(0.26, 1.25)	0.55	(0.23, 1.28)
Hire Age ≥45				
Low	1.64	(0.50, 5.34)	1.23	(0.35, 4.38)
Medium	1.23	(0.07, 21.00)	0.26	(0.03, 2.37)
High	8.62	(1.32, 56.40)	11.60	(1.04, 130.00)

*Low: 0.001 - 5 rads; Medium: 5.001 - 20 rads; High: 20.001 - 75 rads

**CI = Confidence Interval ($\alpha = 0.05$)

Source: Reset from Cookfair et al. 1983.

Note again the absence of commentary on kidney or circulatory changes. Even though the study focused on lung cancer, any serious problems in these areas should have become evident.^(a) Oak Ridge Associated Universities is continuing analysis of this and other populations of workers. The results are still coming in but are beyond the nominal cutoff time for that history. Suffice it to say that there have not been notable surprises. It is truly unfortunate that the information on exposure is so much less complete than that on the health of the workers. Really adequate air concentration measurements were a very late addition to routine operations.

The ORAU-sponsored study and other research should soon provide analyses for worker populations in other uranium processing plants. Future publications will be awaited with considerable interest.

5. Validated?

The early returns indicated serious problems with some of the metabolic constants for uranium, especially those for the respiratory tract and an apparently marked difference in susceptibility of humans compared to animals in the nephrotoxic action of uranium. These differences persist. Possible explanation for the much lower than expected deposition in lung lies in the high density of uranium particles (Eisenbud). Possible reasons for the paucity of findings of kidney damage in humans may lie in the phenomena of developing tolerance to uranium effects, but this is only conjecture.

It cannot be said that recent work has proven these explanations to be fully correct, but it is on the way. On the metabolic side, an entirely new model for uranium has been constructed (see Wrenn 1981; Wrenn, Roswell, and Durbin 1982; Wrenn et al. 1985; Durbin 1986). This involves changes in much more than

(a) One wonders why the study of this important group had to wait so long to begin. In answer to a question from the author, Dr. Cookfair responded that the data could not be released until the processes involved had been changed.

the respiratory-tract deposition constants. Only the future can tell whether or not subsequent autopsy data will confirm the new model. We will look to the USUR for this.

Despite Eisenbud's dramatic story on difference in chemical toxicity between humans and animals, few if any of the current studies are looking very carefully at chemical toxicity of uranium in different species. The emphasis has shifted to correlation with radiation dose, as described in chapter 15 for drinking water standards. The continuation of studies at Oak Ridge and new populations that USUR may identify is needed to nail this down. Meanwhile, it appears that Mont Mason's remark (quoted by Eisenbud [1975]), "We are not at all smug about this—only grateful," seems to characterize the present views toward nephrotoxicity.^(a)

On balance, we must conclude that none of the evidence indicates that the basic standards for exposure to uranium are seriously wide of the mark. There are more puzzling inconsistencies, however, than for many other standards. While reasonable explanations are forthcoming, there is no way to prove retrospectively whether or not they are correct. It will require very carefully planned and executed epidemiologic studies to settle conclusively some of the remaining questions, and these must be done while the exposed populations are still with us.

C. The Fission Products

Most of the work involving the fission products has already been reviewed in chapter 13 since the *raison d'être* was fallout from weapons testing, as well as in chapters 6 and 8. Some of the research is of more or less general applicability to the validation of standards. Some was reviewed in chapter 13 and should be consulted for completeness.

1. Strontium

The isotopes of strontium important to people, ^{89}Sr and ^{90}Sr - ^{90}Y , have been studied in humans primarily by using the convenient short half-life isotope ^{89}Sr . These are exclusively metabolic rather than effects studies, since the doses were all at tracer levels. Nearly all of the work has been since World War II. A large share of the work has emanated from laboratories abroad rather than from those in the United States, except for measurements connected with fallout. A notable exception is the work done by Herta Spencer at the Hines Veterans Hospital in Hines, Illinois, begun by Laszlo and Spencer at the Montefiore Hospital in New York. We will consider it first.

Much of Spencer's work concerned therapeutic removal of alkaline earth metals by chelation. Therefore, a fairly complete bibliography and the substance of the experiments are reserved for chapter 19. We will review here a few of the basic findings.

A useful review by Spencer and colleagues of the ^{89}Sr method and the effects of manipulation of dietary factors, including stable strontium concentration and

(a) Note added in proof: In 1982, Paul Morrow at Rochester completed a study for the NRC that indicated a potential need for lowering the threshold concentration for kidney damage below the current $3\text{ }\mu\text{g/g}$ (Morrow et al. 1982). Since the experiments did not produce steady-state levels, further evaluation is required.

of some hormonal factors, is contained in the *Proceedings of the International Symposium on Some Aspects of Strontium Metabolism* (Lenihan, Loutit, and Martin 1967).

First, the absorption (Spencer, Lewin, and Samachson 1967) was calculated from plasma levels and fecal excretion. The two agreed reasonably well. The average absorption varied among twelve patients from about 35% to about 10%. The authors state the average true absorption of an oral dose is 20%, with 80% unabsorbed and 2.5% passed in the stool as endogenous excretion of ^{85}Sr . The fraction from gastrointestinal tract to blood for all strontium isotopes was given in the ICRP/NCRP 1959 reports as 0.3 (30%). The same value is adopted for soluble salts of strontium in ICRP Publication 30, Part I (1979) but with a reduction to 0.01 (1%) for strontium titanate. Publication 30 gives a range of 0.2 to 0.5 for uptake of soluble salts. No serious problems of validation appear here, especially since the recommended value is higher than that found experimentally in humans by Spencer et al.

Second, the effect of adding stable strontium was to raise the plasma levels of ^{85}Sr . This indicated greater absorption of ^{85}Sr in the presence of stable strontium. If this is a mass effect, it is the opposite of that seen for uranium (see section VI B).

The balance of the review concerns the influence of the many dietary and hormonal factors. There is no doubt but these can play an important role. Any model made for one set of circumstances can be significantly wrong in other circumstances.

At the same symposium, Cyril Comar stressed the need for always paralleling strontium measurements with measurements of calcium. This was reviewed in chapter 13 (Comar 1967). Spencer's work was laced liberally with studies of calcium concentrations and behavior.

Several other U.S. studies in humans are quoted by Comar and Wasserman (1956). They include work from Comar's group and earlier work of Laszlo and Spencer. These include effects of disease processes. The only work with direct bearing on validation concerns the possibility of estimating initial body burden from subsequent excretion curves.

A tenet of the animal work was that strontium remained only briefly in soft tissue and was deposited primarily in bone for any periods beyond a few days. Was this validated in the work with humans? Work from the United Kingdom and other work by Spencer quoted in chapter 19 bears on this question.

Rundo (1967), then at Harwell, measured the retention of ^{85}Sr in the skeletons of two subjects maintained for twenty-one to thirty-two days on a constant diet containing the isotope. He was able to measure skeletal content by in-vivo techniques even when considerable strontium was still in the gastrointestinal tract. From about five days after cessation of intake, virtually all of the strontium was in the skeleton.

The retention function for skeleton as Rundo developed it had three exponential components, which described the retention better than the single component model of ICRP/NCRP. ICRP Publication 30 uses the Marshall model (see section V B), a somewhat more complex representation but not widely different. As usual, a power function could also fit the retention data, as we have seen many times before for other radionuclides. Rundo discards it because it "has no physiological significance."

At the same international meeting, Harrison and Sutton (1967) from the Medical Research Council facility at Harwell presented data on the ratio of fecal

to urinary clearance of strontium in humans. The subjects showed individual differences in the ratio after ingestion in the diet compared to intravenous doses.

Lloyd (1967) found lower renal clearance and less strontium/calcium discrimination in the rabbit than in people.

It can be said that the basic premise that most of long-retained strontium is in bone has been validated in humans. The species differences, variations among human subjects, mode of representation of retention functions, etc., do not invalidate the basic models; but they point to the need for continual updating of models when assessment is needed and the use of data from the individual concerned rather than blanket models designed for the prospective setting of standards.^(a)

In an earlier section of this chapter, we quoted recent work from the University of California at Davis where dose-response relationships for ^{90}Sr and ^{226}Ra were compared in several species, including humans. These, as well as the Utah research, go far toward showing the degree to which the results of long-term animal experiments can be applied to man, in other words their validation vis-à-vis man. It is broadly satisfying but full of differences in detail.

While the coverage above is not complete, it should suffice to show that no large problems have appeared concerning validation of the data for strontium in humans, but they apply only to its metabolism. Thankfully, no exposures to humans have even approached those at which effects would be expected.

2. Iodine

Most of the research with radioiodine has concerned either its uses in medicine or environmental contamination problems. The former appears in chapter 20; the latter has already been discussed in chapters 9, 10, and 13.

There is no question about iodine concentrating almost exclusively in the thyroid in humans as it does in animals. The biological and effective half-lives have been tied down by innumerable clinical measurements.

The largest problem with validation of the old standards for iodine came in terms of environmental transport and population exposure standards. As we saw earlier, the practice used by both the advisors (see section II A) and the regulators (e.g., The Code of Federal Regulations) was to devise population standards by use of a scaling factor from the occupational standard. Careful analysis of the plant-food-cow-milk-human chain done as part of the research stimulated by fallout showed that the standard scaling factor was totally inapplicable to populations exposed to iodine through this chain. This led, as described earlier, to reduction of the allowable discharges of iodine by a factor of seven hundred (rounded off to one thousand). Research in man played only a small part in this process. However, the entire chain could be said to have been a part of the validation of the old standard.

D. Other Radionuclides

Data on humans useful for validation of standards are not numerous for radionuclides outside of the three major classes discussed so far in this section—

(a) Unfortunately, the current regulatory climate tends to inhibit the application of idiosyncratic data, even though it may be scientifically justifiable and technically impeccable.

actinides, uranium, and fission products. The exception is the gaseous elements like tritium, the noble gases, etc.

Because of its importance in both fission and fusion, tritium has received some attention that might be called "validation." One example is work by Osborne (1972) at the Chalk River installation of Atomic Energy of Canada, Ltd. Osborne considers the physiology of tritium, the types of exposure, and the pertinent parameters to determination of permissible levels. He overtly compares the experimentally determined parameters with the ICRP/NCRP (1959) parameters and calculations. He reviews most of the considerations we saw in chapter 10. The role of the tritium bound to tissue components receives special attention, as it should.

Osborne concludes that current limiting levels in air, drinking water, and food, as well as the choice of body water as the critical tissue, are all conservative. He does not indicate *how* conservative. Apropos the nagging problem of tritium in DNA, he estimates (along with others we have met in chapter 10 and will in chapter 20) that less than 0.2% of the initial dose rate to the nucleus is from tritium in DNA, and the annual genetic dose is about 0.3 mrem. Thus, it appears that once we took account of skin absorption of tritium (chapter 10), the standards for tritium had been validated amply.

Validation of the original standards can be viewed as reasonably good for the noble gases as well, as emphasized by Osborne for tritium. Information is still needed on other substances, particularly environmental transport parameters.

A final bit of validation concerns barium. Research by Newton, Rundo, and Harrison (1977) at the AERE, Harwell found good support for the ICRP alkaline earth model (The Marshall model) using data on ^{133}Ba in a sixty-year old man.

Space prohibits further exploration of this type of work. The nature of the research, its locales, and the extent of validation should be clear from what has been said.

VIII. Epilogue

There is little doubt that the research information developed for radionuclides played an important part in the development of standards for limiting exposure. The mere bulk of this chapter should testify to that. Nor can it be denied that large portions of the experimental work had as an ultimate, frequently a primary, goal the development of information applicable to the standard-setting process. The standard for ^{226}Ra was as closely coupled to overt experience of effects in humans as any radiation standard we have. The complex computational schemes and the many models were entirely dependent upon the metabolic data produced in the researches we have reviewed. Need we say more? I am afraid we must.

As discussed briefly in earlier parts of this chapter, the standard-setting process has many facets. It inevitably involves judgment, selection, and many factors totally outside of biology and medicine. Even the radium standard involved judgment by using a factor of ten below the body burden at which effects first appeared and the subjective decision as to whether or not one would be content to have his own wife or daughter carry a burden of $0.1\ \mu\text{Ci}$ of ^{226}Ra . The selection of metabolic factors always required a judgment. As discussed earlier in the chapter, selections were made for a "best" figure for the situation at hand. They were not averages or any other statistically based figure.

When we depart from the radium standard as a base, the primary standards for radionuclide exposure have been based upon the maximum permissible dose of external radiation. This was selected in a highly judgmental manner. It is difficult to trace the exact steps leading to its selection. Although it has served us well, it would be a gross overstatement to indicate that it had been derived by a purely scientific process starting from first principles.

A most interesting analysis of the history of radiation protection before World War II was developed by Daniel P. Serwer at Brookhaven National Laboratory under the title "BEAG" (Serwer 1976). The report analyzes the role of social pressures, professional groups, and to a lesser extent economic factors in the practices of radiation protection in the period discussed. Unfortunately, science comes out second best for the primary standards.

This phenomenon is not limited, of course, to radiation standards. Purely scientific facts were given an even less central role in most of the early standards for chemical toxins than Serwer concludes is true for radiation standards. Nevertheless, it was the scientific information that began the process. It just got mixed in with many other processes along the way.

As our ideas of what is acceptable have urged even lower standards, and as the linear no-threshold concept took over the thinking and implied that there was no completely "safe" dose, the role of the purely scientific process has become even more difficult. Indeed, it seems unlikely that there could ever be a scientific experiment or process of sufficient size or complexity to determine quantitatively the effects on populations of the very low radiation doses now being considered as potential limits. As the uncertainty rose, so did the controversy and the opportunity for nonscientific aspects to assume control.

Recently, Crandall and Lave have edited a book prepared by the Brookings Institution in Washington entitled, *The Scientific Basis of Health and Safety Regulations* (Crandall and Lave 1981). This is not aimed at radiation regulation, but the processes chosen are comparable. Using five case studies and expert groups to comment on each, they conclude that scientific data and their analysis now play a minor role in the setting of primary standards. In a scathing indictment of some of the regulators, the following appears "... An agency may exacerbate concern about a trivial or non-existent problem ... Standards are enacted on the basis of only fragmentary evidence of a potential Health or Safety Hazard. ..." (From Thomas's 1983 review of the Crandall and Lave book).

Does this mean we have been wasting our time and resources? It does not! First, the fund of scientific information in the radiation field far exceeds any other. We have the best chance of having pertinent scientific facts. Second, it is only in the setting of the *primary* standard that the nonscientific aspects enter. Once that is established, the myriad computations and models for radionuclides in both humans and the environment must be brought into action. The scientific and technical data are absolutely essential for these; they will continue to be.

Currently there is a strong tendency to base standards on risk rather than dose. To do this, the conventional dose-response curves have been translated into dose-risk curves. But this usually still requires calculation of dose and knowledge of radionuclide behavior. A pure risk approach, i.e., one that goes directly from intake or body burden to risk, is much to be desired. It is possible to do this for a few radionuclides, e.g., ^{226}Ra . As research continues, it may be possible for more. However, the time is far off when standards for all radionuclides can be determined without the intermediary steps of dosage calculation.

One important area that has been somewhat neglected until recently is one that is basic to the application of a primary radiation standard derived from experience with external radiation to those for radionuclides. Does a given absorbed dose have the same effectiveness, i.e., produce the same risk, whether delivered by x-ray photons or a deposited beta-emitting radionuclide? Broadly speaking they should be. An erg is an erg. But it is not so simple. Microdistribution of radionuclides and of radiation dose can enter the picture, as can other factors. A survey of this question by the NCRP committee cited earlier indicates already some possible exceptions, e.g., the longer-lived iodine isotopes. There may be more.

Finally, it will be noted that we have said relatively little about details of establishment of the primary standards for radiation exposure. These have been and are being competently dealt with by others. It should be obvious from the materials reviewed in this chapter, bona fide research of the most open kind, that radiation standards as they now exist have been broadly validated. It seems most unlikely that a large systematic error could have survived such careful scrutiny. No doubt there are many areas that need further work, but these are minor compared to the major unfinished business in the field of chemical toxicology and environmental pollution with toxic chemicals. Let us hope that the experience gained in setting radiation standards can be helpful in the enormous task we all face in this other arena. Let us hope, too, that perspective is maintained and radiation standards not reduced unduly by either scare tactics or a "because you can do it, you must do it" philosophy.

Important research is still needed for the development of still better standards for radionuclides, even though most of the standards have either been reasonably well validated, or reasonable explanations have been developed in the case of significant discrepancies. A system based upon direct estimation of risk is being explored by the NCRP.

IX. Summary and Commentary

This chapter reviews in a general way how the findings from the research laboratories and field experiences contributed to the process of setting limits for the intake of radioactive materials by humans. It is not a formal history of radiation protection standards. That has been and is being done very adequately by others. It does concern the use made of the information gained in the research programs, most of them reviewed in this book. In addition, there is discussion of those efforts made by the biomedical community toward validation of standards already set.

The organizations that now carry, or at some time carried, responsibility are detailed both for orientation and to highlight their contributions. The latter applies especially to the Tri-Partite Conferences on Internal Dosimetry held in the late 1940s and the work of the U.S. Federal Radiation Council. These, plus the many organizations still functioning, are listed with a short summary of the nature of their activities. All are considered as advisors, even some activities of the Congress of the United States. The regulators, state and federal, are also reviewed in broad terms.

Two quite separate systems have been used to arrive at standards for intake of radionuclides: (1) direct derivation from human experience modified by animal data and (2) computation of an intake limit based on a radiation dose

comparable to that allowed from external sources of radiation. Types of information and types of research applicable are quite different by the two methods.

The best example of direct derivation is the designation of the maximum permissible body burden of ^{226}Ra and calculated secondary standards for it. For this, the accumulated information from human experience, the radium dial painters and radium chemists and the patients that received radium as a therapeutic nostrum, led directly to a standard. Based on examination of records through 1940, it was determined that no significant health effects had been seen in individuals carrying body burdens of ^{226}Ra less than $1\ \mu\text{Ci}$. The standard became $0.1\ \mu\text{Ci}$ by insertion of a safety factor of ten, and it was promulgated in 1941. Although much more information has been accumulated in the intervening years, nothing has happened to question the validity of this first standard for a radionuclide.

The standard for ^{239}Pu was based on the radium standard. It used the ratio of effectiveness of ^{239}Pu to ^{226}Ra determined in the several experiments described in earlier chapters. It calculated a maximum permissible body burden by modifying the radium standard by the relative toxicity (relative effectiveness) ratio. This standard was developed during and at the end of World War II and has been strengthened by postwar research.

The first standard for ^{222}Rn was developed at the same time as the one for ^{226}Ra . It was comparable to most industrial hygiene standards in that it was based on measurements of air concentrations that, over long exposure periods, were not associated with demonstrable effects. Because of the short half-life of radon and its daughters, there was no way to determine corresponding body burdens. This standard was intended for application to work rooms. As described in chapter 3, the problems of radon exposure in mines required a more complex system whose genesis and characteristics are described there.

Exposure to natural uranium is another example of direct derivation. Only in this case it was a direct determination from the data obtained in animal exposures. The experiments are described in chapters 2 and 9. Despite the thousands of exposures of humans to natural uranium, it is too weakly radioactive to have produced, at the levels involved, obvious long-term radiation effects, and the evidence of chemical toxicity in workers has been evanescent. At the beginning, the uranium standard was linked by analogy to lead, but, as the animal work progressed, direct derivation was possible with, of course, suitable safety factors. As hinted at above, uranium exposures carry a dichotomy. With soluble compounds that are readily transported and excreted, chemical toxicity to the kidney tubules controls exposure. With very insoluble compounds, it can be calculated that radiation exposure might control. However, it took the heroic experiment described in chapter 2 to cram enough uranium into the lung and have it stay long enough to produce clear-cut radiation effects. None of the animal data used for deriving the earlier uranium standards showed anything but chemical toxicity.

A few other radionuclides can be considered to have had their standards derived directly from effects in humans or animals. Radium-224, the isotope of radium used in Germany over the period 1944 to 1951, generated data in humans sufficient to support a standard by comparison with ^{226}Ra . However, the use of ^{224}Ra was discontinued almost before this information could be generated, and it has been more useful for other purposes.

A final case of potential direct derivation is ^{232}Th in Thorotrast. As described in chapter 4, there is a large population of individuals who received Thorotrast

as a radiopaque medium, and this population is developing liver tumors. However, there were some complexities, and the operating standards for ^{232}Th were not derived directly. It now appears that the complexities have been solved, and we can look forward to future derivation of a thorium standard from the thorium organ burden in these populations.

The enormous expansion in the number of radionuclides to which people might be exposed required a different approach to standards—termed here the computational approach. There was obviously not enough information on effects for the majority of the newly developed radioactive materials to support direct derivation of standards. Instead, the maximum permissible dose rate to various organs, including the whole body, derived from experience with external radiation sources, was utilized. These had been developed from many years of experience with x and gamma rays and other radiation types from sources external to the body. This approach began officially at the Tri-Partite Conferences, but was in operation earlier in individual laboratories.

The accumulated metabolic information on a large number of radionuclides could be used for computing the dose to the target organ. Others could be computed by comparison to their chemical analogues. Reports were developed beginning in the 1950s giving a maximum permissible body burden, organ burden, and maximum allowable concentrations in air and water for hundreds of radionuclides. Recently, the ICRP has prepared a huge compendium listing secondary standards such as annual limits on intake, derived air concentrations, etc., for over seven hundred radionuclides. All of these are based upon the primary standard for external radiation exposure (the direct route was not used by ICRP in this latest version). In addition to physical characteristics, such as decay scheme and constants, biological retention in many organs, the relative concentrations in many organs, and general models for behavior in the lung and the gastrointestinal tract had to be determined and used. Thus, most of the enormous effort describing “metabolism” (i.e., pharmacokinetics) of radionuclides described in earlier chapters was brought to bear on the setting of standards. Details of the system and its variations and of the models are given in the chapter.

The converse of the use of the research data in setting standards is its utility in checking the validity of standards already set. Obviously, many standards had to be set with tenuous and preliminary information. The accumulated information from larger and longer-term efforts has been very useful in this validation process. The lack of demonstrable effects in humans from plutonium, uranium, strontium, and related radionuclides constitute, to a degree, a validation of the standards under which we have been working. However, the populations are small, and satisfactory epidemiology for many important elements is still in the future. The notable exception is ^{226}Ra , for which both the number and consistency of the follow-up cases can be viewed as ample validation of the original standard.

The large studies of lung cancer in uranium miners have provided both epidemiologic bases for the standards used and validation of some of the parameters used. Unfortunately, the problems of dose measurement and dose calculation have made the story more complex than for some other radioisotopes.

Another type of validation in man is seen in the several experiments with human subjects detailed in other chapters. These were metabolism experiments. The similarities of pharmacokinetics seen in humans to the much larger body of

information from animals can be regarded as validation for man of the use of the best of the data from animal studies.

Further validation of both standards and of various metabolic models and single parameters can be expected from the work of the U.S. Transuranium Registry and the U.S. Uranium Registry and the ongoing studies of the radium patients and the plutonium workers, plus a few new epidemiologic studies in populations exposed many years ago.

While it can be said that current data validate, in broad terms, the standards set and the important parameters of distribution, retention, and excretion, many details require clarification. Many models are very approximate. The validity of using the dose rate derived from external radiation sources for limiting internally deposited radionuclides depends upon there being no difference in effectiveness of a given dose under the different conditions. Only a few radionuclides have been examined critically in this regard with some, but not large, differences seen in certain cases.

Despite the ever-present needs for more information, it can be said that the researches described in this book played a key role in the derivation and/or implementation of standards for radioactive materials deposited in the body and their validation.

Note 1(a)

ICRP (1959) formulation for determination of the maximum permissible body burden (q) of radionuclides that deposit in bone:

$$q = \frac{q^{Ra} f_2^{Ra}}{f_2} \times \frac{\epsilon^{Ra}}{\epsilon} = \frac{0.1 (0.99)}{f_2} \times \frac{110}{\epsilon} = \frac{11}{f_2 \epsilon}$$

in which $q^{Ra} = 0.1 \mu\text{C}$ is the maximum permissible body burden of Ra^{226} ;

f_2 = fraction of radionuclide in the skeleton of that in the total body;

$f_2^{Ra} = 0.99$ is the value of f_2 for radium;

ϵ = effective absorbed energy per disintegration of a radionuclide = $\Sigma EF(RBE)n$; $\epsilon^{Ra} = 110$ is the value of ϵ for radium;

E = energy (MeV) deposited in skeleton per disintegration;

RBE = relative biological effectiveness = 1 for α , γ , β^- , β^+ , e^- , (it is set equal to 1.7 if the maximum energy, $E_m \leq 0.03$ MeV for β^- , β^+ or e^-), 10 for α and 20 for recoil atoms;

F = ratio of disintegrations of daughter to disintegrations of parent.

It is assumed that 99 per cent of the radium in the body is in the skeleton, and the total energy deposited in the skeleton per disintegration of Ra^{226} plus 30 per cent of its daughter products is 11 MeV, and thus the effective energy deposited in the skeleton is $\Sigma EF(RBE)n = 110$. For other radionuclides which are localized in the bone, the effective absorbed energy is found from $\Sigma EF(RBE)n$. (b)

(a) This approach and formulation were abandoned in the ICRP Report 30 (ICRP 1979). However, it was used for many years and is so important to the derivation of standards from the research data that we reproduce it anyway.

(b) As described elsewhere in this chapter, the value of n is taken as 1 if the radionuclide or its progenitor is an isotope of radium, as 5 for all other cases.

Note 2

ICRP (1959) formulation for calculating maximum permissible body burden (q) on the basis of the permissible dose rate to the critical body organ: (a)

The equation for maximum permissible body burden, q , based on a maximum permissible dose rate, R rem/week, is

$$q = \frac{100 \text{ mR}}{3.7 \times 10^4 \times 1.6 \times 10^{-6} \times 6.05 \times 10^5 f_2 \epsilon}$$

$$q = \frac{2.8 \times 10^{-3} \text{ mR}}{f_2 \epsilon}$$

and when $R = 0.3$ rem/week

$$q = \frac{8.4 \times 10^{-4} \text{ m}}{f_2 \epsilon}$$

where 3.700×10^4 = dis/sec per μC ;
 1.6×10^{-6} = ergs/MeV;
 6.05×10^5 = sec/week;
 100 = ergs/g per rad;
 m = mass of the organ of reference (g);
 and ϵ is defined [as in note 1 above].

To derive concentrations in air and water for critical organs other than the gastrointestinal tract the following relationships were used. It was assumed that radioactive material is taken up by the critical body organ at the rate of P $\mu\text{Ci/day}$ and that the biological elimination follows a simple exponential law. Thus:

$$\frac{d(q f_2)}{dt} + \lambda(q f_2) = P$$

The solution with $q f_2 = 0$ when $t = 0$ is $q f_2 = P(1 - e^{-\lambda t})/\lambda$

in which $q f_2$ = burden of the radionuclide in the critical body organ (μC);
 f_2 = fraction of radionuclide in critical organ of that in total body;
 λ = effective decay constant = $0.693/T$;
 T = effective half-life $(T_r T_b)/(T_r + T_b)$ (days);
 T_r = radioactive half-life (days);
 T_b = biological half-life (days);
 t = period of exposure; for occupational exposure $t = 50$ years (in the early publications of NCRP and ICRP t was set to equal 70 years);

P = rate of uptake of the radionuclide by the critical body organ ($\mu\text{C/day}$) = $(M)S$, where M is the concentration ($\mu\text{C/cm}^3$) of the radionuclide in water or in air taken into the body, and S is the product of the average rate of intake (cm^3/day) of water or of air and the fraction of the microcuries arriving in the critical body organ. For occupational exposure at the maximum permissible concentration (MPC) of the radionuclide in water, $M = (\text{MPC})_w$ and in air, $M = (\text{MPC})_a$. In a 24 hr day, the standard man . . . consumes 2200 cm^3 of water and breathes $2 \times 10^7 \text{ cm}^3$ of air. Because of his greater activity during an 8 hr work day, it is assumed that half of this body intake occurs during the work period, viz. 1100 cm^3 of water and 10^7 cm^3 of air. The work schedule for the standard man is 8 hr/day, 5 days/week and 50 weeks/year. Therefore for the average occupational exposure, $S = 1100 \times 5/7 \times 50/52 f_w = 750 f_w \text{ cm}^3$ of water per day and $S = 10^7 \times 5/7 \times 50/52 f_a = 6.9 \times 10^4 f_a \text{ cm}^3$ of air per day.

(a) In the 1979 ICRP formulations, much of this terminology was changed, and the concept of maximum permissible body burden was abandoned. Yet, the principles have not changed drastically.

Note 3

Selected publications on trace metals in human tissues by Isabel H. Tipton and colleagues, University of Tennessee and Oak Ridge National Laboratory^(a)

- Spectrographic Analysis of Trace Elements in Human Tissue. *Phys. Rev.* 87 (1952).
- Spectrographic Analysis of Human Tissue, *Phys. Rev.* 91:214, with Foland, Bobb, and McCorkle (1953).
- Spectrographic Determination of Trace Elements in Human Tissue*, ORNL-CF-53-8-4, with Foland, Bobb, McCorkle, et al. (1953).
- Spectrographic Analysis of the Tissues from Autopsies of Twenty-four Instantaneous Deaths*, ORNL-CF-54-12-66, with Steiner, et al. (1954).
- Methods of Collection, Preparation, and Spectrographic Analysis of Human Tissues*, ORNL-CF-57-2-2, with Cook, Steiner, et al. (1957).
- Spectrographic Analysis of Normal Human Tissue from Baltimore, Maryland* ORNL-CF-57-11-33, with Cook, Steiner, Foland, et al. (1957).
- Spectrographic Analysis of Normal Human Tissue from Seattle and Tacoma, Washington*, ORNL-CF-58-10-15, with Cook, Foland, et al. (1958).
- Spectrographic Analysis of Normal Human Tissue from Richmond, Virginia*, ORNL-CF-59-8-106, with Cook, Foland, et al. (1959).
- The Distribution of Trace Metals in the Human Body. In *Metal Binding in Medicine*, Chapter 3, edited by M. J. Seven, J. B. Lippincott Company (1960).
- Variability in the Metal Content of Human Organs, *J. Lab. and Clin. Med.* 60:245, with Perry, Schroeder, and Cook (1962).
- Trace Elements in Human Tissue. Part I. Methods. *Health Phys.* 9:89-101, with Cook, Steiner, Boye, Perry, and Schroeder (1963).
- Trace Elements in Human Tissue. Part II. Adult Subjects from the United States. *Health Phys.* 9:103-145, with Cook (1963).
- Trace Elements in Human Tissue. Part III. Subjects from Africa, the Near and Far East, and Europe. *Health Phys.* 11:403, with Schroeder, Perry, and Cook (1965).
- Trace Elements in Diet and Excreta, *Health Phys.* 12:1683-1689, with Stewart and Martin (1966).
- Elemental Composition of Standard Man*. Health Physics Division Annual Progress Report, ORNL-4007, with Snyder and Cook (1966).
- Long Term Study of Intake and Excretion of Stable Elements*. Health Physics Division Annual Progress Report ORNL-4168,283, with Stewart (1967).
- The Variation with Age of Elemental Concentrations in Human Tissue, *Proceedings, First International Congress of Radiation Protection*, Rome 1: 759-767, with Johns and Boyd (1968).
- Trace Metals in Man: Strontium and Barium. *J. Chron. Dis.* 25:491-517, with Schroeder and Nason (1972).
- Report of the Task Group on Reference Man*. Isabel Tipton was a member of the Task Group of Committee 2 of the International Commission on Radiological Protection that prepared the Reference Man report (ICRP 1975).

Note 4

Summary of Alkaline Earth Model, Condensed from ICRP Publication 20 (ICRP 1973)^(b)

Retention in bone volume is described by two functions, one for compact bone and one for cancellous bone. They are respectively:

$$R_{\text{COMPVOLUME}} = p\beta\epsilon^b(t + \theta)^{-b} e^{-r\lambda t}$$

$$R_{\text{CANVOLUME}} = p(1 - \beta)\epsilon^b(t + \theta)^{-b} e^{-\sigma r\lambda t}$$

Theta (θ) is a time-dependent factor which is defined in terms of the whole-body retention function, R:

$$\theta = [f_C 0.8 c\lambda\omega(1 - R)/p\epsilon^b\beta\eta k]^{-1/b}$$

$$R = (1 - p)e^{-mt} + p\epsilon^b(t + \epsilon)^{-b}[\beta e^{-r\lambda t} + (1 - \beta)e^{-\sigma r\lambda t}]$$

(a) A complete bibliography can be supplied to interested readers.

(b) Printed also in *Health Phys.* 24:125-221, 1972.

Total bone surface retention is defined as the solution to the following differential equation:

$$dR_{\text{SURFACE}}/dt = \lambda_{\text{SUR}} (C_{\text{SURFACE}} S - R_{\text{SURFACE}})$$

where S is the fraction of injected activity per gram calcium in the blood plasma; S is related to the whole-body retention function by $S = (-1/\eta k)(dR/dt)$. Retention on cancellous bone surfaces = $\frac{1}{2} R_{\text{SURFACE}}$ and retention on compact bone surfaces = $\frac{1}{2} R_{\text{SURFACE}}$.

The retention functions exclude the effect of radioactive decay and assume that a single intravenous injection has been made. The parameters take on different values for Ca, Sr, Ba and Ra, which are given in Table 27 of ICRP Publication 20.

Parameters not defined above are:

- b = power function slope
- β = fraction of bone volume activity deposited in compact bone
- C = whole-body or total bone calcium
- C_{SURFACE} = calcium content of bone surface pool
- ϵ = time at which the extrapolated whole-body retention is equal to p . (Sometimes called power function time shift.) Is related to turnover time of the initial pool.
- η = excretory discrimination factor for given alkaline earth relative to calcium
- f_C = ratio of total activity deposited in compact bone volume to that in new compact bone
- k = rate of endogenous calcium excretion (urine + feces)
- λ = apposition-resorption rate of compact bone
- λ_{SUR} = rate constant of bone surface pool
- ϕ = fraction of whole-body retention function, R , not in the early exponential term
- r = recycling correction

Translated to a whole-body retention function, the following expression applies:

$$R = (1-p)e^{-mt} + pe^{b(t+\epsilon)-b[\beta e^{-r\lambda t} + (1-\beta)e^{-\sigma r\lambda t}]}$$

where R = the fraction of the injected activity remaining in the body following a single intravenous injection (not including radioactive decay),

ϵ = a small time (0.3–3 days), related to the turnover of an initial pool,

b = power function slope (0.1–0.5), related to diffusion of activity from bone to blood and excretion of part of that activity from the body,

λ = the rate of apposition and resorption in compact bone (2.5%/year),

σ = the ratio of the turnover rates of cancellous and compact bone, (4),

β = the fraction of bone volume activity deposited in compact bone (~ 0.5),

r = a factor which corrects for redeposition of activity in new bone at sites of resorption long after injection (0.83–0.99),

m = the rate constant of a small early exponential in R (0.1–0.8 day⁻¹),

p = the fraction of R not in the early exponential (0.6–0.8),

t = time (from 0 to any time after injection).

This is a six-parameter model of bodily retention because β and r follow from the other parameter values. The time derivative and integral of R are used together with additional parameters to generate consistent internal retention functions for bone surface, new and old compact and cancellous bone, blood, and soft tissue. The bone functions explicitly separate loss of activity by diffusion (diminution) from that by resorption. All the retention functions are assumed to be age-invariant, so that time integrals may be used to simulate the results of any schedule of radioactive intake into the blood, whether from injection, lung, or diet.

Note 5

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References

- American Physiological Society Handbook*. [A nine part, 24 volume series of publications produced by the American Physiological Society beginning in the late 1950s and updated beginning in 1977.] Baltimore, Md.: Williams & Wilkins Company.
- Anspaugh, L. R., W. L. Robison, W. H. Martin, and O. A. Lowe. 1971. *Compilation of published information on elemental concentrations in human organs in both normal and diseased states*. [In three parts.] UCRL-51013, pts. 1, 2, and 3. Livermore, Calif.: Lawrence Radiation Laboratory.
- APS. See American Physiological Society.
- Archer, V. E., J. K. Wagoner, and F. E. Lundin, Jr.. 1973. Cancer mortality among uranium mill workers. *J. Occup. Med.* 15:11-14.
- Auerbach, S. 1970. Ecological considerations in siting nuclear power plants: The problem of long-term biotic effects. In Foreman 1970, pp. 29-44.
- Beck, W. L., D. L. Cookfair, C. L. Sowder, and K. Gissel. 1983. Radiation dosimetry for epidemiologic lung cancer study. In *Epidemiology applied to health physics*, CONF-830101, pp. 436-43. Proceedings of the 16th mid-year topical symposium of the Health Physics Society held in Albuquerque, January 1983. Springfield, Va.: National Technical Information Service.
- BEIR. See Biological Effects of Ionizing Radiations.
- Bell, R. I. 1977. *Radiation protection standards chronology*. Privately printed under auspices of Auburn Univ., Auburn, Ala.: Office of Radiological Safety.
- Bernard, S. P. 1981. An urn model approach to actinide metabolism. In *Actinides in man and animals*, ed. M. E. Wrenn, pp. 607-16. Proceedings of the Snowbird actinide workshop in Snowbird, Utah, October 15-17, 1979. Salt Lake City: RD Press.
- Biological Effects of Ionizing Radiations. 1980. *The effects on populations of exposure to low levels of ionizing radiation: 1980*. BEIR committee, U.S. National Academy of Sciences-National Research Council. Washington, D.C.: National Academy Press.
- Boecker, B. B., R. G. Thomas, and R. O. McClellan. 1977. Accumulation and retention of ¹³⁷Cs-labelled fused aluminosilicate particles by beagle dogs after repeated inhalation exposures. In *Inhaled particles IV*, ed. W. H. Walton, pt. 1, pp. 221-36. Proceedings of an international symposium held in Edinburgh, September 22-26, 1975. Oxford: Pergamon Press.
- Bruner, H. D. 1968. A plutonium registry. In *Diagnosis and treatment of deposited radionuclides*, eds. H. A. Kornberg and W. D. Norwood, pp. 661-65. Proceedings of the 7th annual Hanford biology symposium held in Richland, Wash., May 15-17, 1967. Amsterdam: Excerpta Medica Foundation.
- Cantril, S. T. and H. M. Parker. 1945. *The tolerance dose*. Manhattan District report MDDC-1100. Oak Ridge, Tenn.: Oak Ridge Associated Universities, Technical Information Division.

- Cheremisinoff, P. M. and A. C. Morresi. 1977. *Environmental assessment and impact statement handbook*. Ann Arbor, Mich.: Ann Arbor Science (4th printing 1980).
- Cohn, W. E. 1948 and 1980. Toxicity of inhaled or ingested radioactive products. *Nucleonics* 3(1):21-26. Reprinted as a landmark paper with comments by J. N. Stannard in *Health Phys.* 38:1015-20.
- Comar, C. L. 1967. Some principles of strontium metabolism: Implications, applications, limitations. In Lenihan, Loutit, and Martin 1967, pp. 17-31.
- Comar, C. L. and R. H. Wasserman. 1956. Radioisotopes in the study of mineral metabolism. In *Progress in nuclear energy*, series VI, Biological science, vol. 1. pp. 153-96. London-New York: Pergamon Press.
- Commoner, B. 1970. Nuclear power: benefits and risks. In Foreman 1970, pp. 224-55.
- Cook, M. J., K. Z. Morgan, and A. G. Barkow. 1956. Experiment designed to test the validity of the current practice of using single-exposure data to calculate maximum permissible concentration in water for continuous exposure to radioisotopes. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* 75:1177-87.
- Cookfair, D. L., W. L. Beck, C. Shy, C. C. Lushbaugh, and C. L. Sowder. 1983. Lung cancer among workers at a uranium processing plant. In *Epidemiology applied to health physics*, CONF-830101, pp. 389-406. Proceedings of the 16th mid-year topical symposium of the Health Physics Society held in Albuquerque, January 1983. Springfield, Va.: National Technical Information Service.
- Crandall, R. W. and L. B. Lave, eds. 1981. *The scientific basis of health and safety regulations*. Washington, D.C.: The Brookings Institute.
- Cross, F. T. 1979. Exposure standards for uranium mining. *Health Phys.* 37:765-72.
- Cuddihy, R. G. 1981. Modeling the metabolism of actinide elements. In *Actinides in man and animals*, ed. M. E. Wrenn, pp. 617-28. Proceedings of the Snowbird actinide workshop held in Snowbird, Utah, October 15-17, 1979. Salt Lake City: RD Press.
- Darby, S. C. and J. A. Reissland. 1981. Low levels of ionizing radiation and cancer: Are we underestimating the risk? *J. R. Statist. Soc. A* 144(3):298-331.
- DBER. See Division of Biological and Environmental Research.
- Diel, J. H. and D. L. Lundgren. 1982. Repeated inhalation exposure of beagle dogs to $^{239}\text{PuO}_2$: Retention and translocation. *Health Phys.* 43:655-62.
- Division of Biological and Environmental Research. 1974. Report of ad hoc committee convened May 22, 1974. U.S. Atomic Energy Commission. [Viewed courtesy of Department of Energy.]
- Dolphin, G. W. and I. S. Eve. 1966. Dosimetry of the gastrointestinal tract. *Health Phys.* 12:163-72.
- Donoghue, J. K., E. D. Dyson, J. S. Hislop, A. M. Leach, and N. L. Spoor. 1972. Human exposure to natural uranium. A case history and analytical results from postmortem tissues. *Br. J. Ind. Med.* 29:81-89.
- Durbin, P. W. 1971. *Plutonium in man: A twenty-five year review*. UCRL-20850. Berkeley, Calif.: Lawrence Radiation Laboratory.
- Durbin, P. W. 1972. Plutonium in man: A new look at the old data. Chapter 7.2 in *Radio-biology of plutonium*, eds. B. J. Stover and W. S. S. Jee, pp. 469-530. Salt Lake City: The J. W. Press.
- Durbin, P. W. 1976. Personal communication.
- Durbin, P. W. 1986. Metabolic models for uranium. In *Biokinetics and analysis of uranium in man*, ed. R. H. Moore, USUR-05, HEHF-47, pp. F-1-F-65. Proceedings of a workshop sponsored by the U.S. Uranium Registry held in Richland, Wash., August 8-9, 1984. Richland, Wash.: Hanford Environmental Health Foundation.
- Eisenbud, M. 1970. Standards of radiation protection and their implications for the public's health. In Foreman 1970, pp. 73-89.
- Eisenbud, M. 1975. Early occupational experience with uranium processing. In *Conference on occupational health experience with uranium*, ERDA-93, pp. 8-24. Held in Arlington, Va., April 28-30, 1975. Washington, D.C.: Energy Research and Development Administration.

- Eisenbud, M. and J. A. Quigley. 1956. Industrial hygiene of uranium processing. In *Proceedings of the international conference on the peaceful uses of atomic energy*, vol. 13, pp. 222-28. Held in Geneva, August 8-20, 1955. New York: United Nations.
- Energy Research and Development Administration. 1975. *Conference on occupational health experience with uranium*, ERDA-93. Held in Arlington, Va., April 28-30, 1975. Washington, D.C.
- Environmental Protection Agency. 1976. *Quality criteria for water*. Washington, D.C.: Office of Water and Hazardous Materials. [Note: This document omits discussion of radionuclides. These were reserved for special consideration. These are found in issues of the *Federal Register* and as Appendix B to an undated document entitled *National Interim Primary Drinking Water Regulations*, EPA-570/9-76-003.]
- EPA. See Environmental Protection Agency.
- ERDA. See Energy Research and Development Administration.
- Evans, R. D. 1967a. Statements at U.S. Congressional hearings on "Radiation exposure of uranium miners." In *Congressional hearings 1967*, pt. 1, pp. 655-58. Washington, D.C.: U.S. Government Printing Office.
- Evans, R. D. 1967b. The radium standard for boneseekers—Evaluation of the data on radium patients and dial painters. *Health Phys.* 13:267-78.
- Evans, R. D. 1980. Origin of standards for internal emitters. In Kathren and Ziemer 1980, pp. 141-57.
- Evans, R. D. 1981. Inception of standards for internal emitters, radon, and radium. *Health Phys.* 41:437-48.
- Evans, R. D. 1983. Telephone conversation, March 1983.
- Evans, R. D. and C. Goodman. 1940 and 1980. Determination of the thoron content of air and its bearing on lung cancer hazards in industry. *J. Ind. Hyg. Toxicol.* 22:89-99. Reprinted as a landmark paper with comments by J. N. Stannard in *Health Phys.* 38:919-28.
- Eve, I. S. 1966. A review of the physiology of the gastrointestinal tract in relation to radiation doses from radioactive materials. *Health Phys.* 12:131-61.
- Federal Radiation Council. 1960. *Background material for the development of radiation protection standards*. Report no. 1 of the FRC, May 13, 1960.
- Federal Radiation Council. 1961. *Background material for the development of radiation protection standards*. Report no. 2 of the FRC, September 1961.
- Federal Radiation Council. 1962. *Health implications of fallout from nuclear weapons testing through 1961*. Report no. 3 of the FRC, May 1962.
- Federal Radiation Council. 1963. *Estimates and evaluation of fallout in the United States from nuclear weapons testing conducted through 1962*. Report no. 4 of the FRC, May 1963.
- Federal Radiation Council. 1964a. *Background material for the development of radiation protection standards*. Report no. 5 of the FRC, July 1964.
- Federal Radiation Council. 1964b. *Revised fallout estimates for 1964-1965 and verification of the 1963 predictions*. Report no. 6 of the FRC, October 1964.
- Federal Radiation Council. 1965. *Background material for the development of radiation protection standards: Protective action guides for strontium-89, strontium-90, and cesium-137*. Report no. 7 of the FRC, May 1965.
- Federal Radiation Council. 1967. *Guidance for the control of radiation hazards in uranium mining*. Report no. 8 of the FRC, revised September 1967.
- Federal Radiation Council-National Academy of Sciences. 1964. *Implications to man of irradiation by internally deposited strontium-89, strontium-90, and cesium-137*. Report of an advisory committee of the National Academy of Sciences, Division of Medical Sciences to the Federal Radiation Council, December 1964.
- Federal Radiation Council-National Academy of Sciences. 1966. *Pathological effects of thyroid irradiation*. Revised report of an advisory committee of the NAS, Division of Medical Sciences to the FRC.
- Federal Radiation Council-National Academy of Sciences. 1968. *Radiation exposure of uranium miners*. Report of an advisory committee of the NAS, Division of Medical Sciences to the FRC, August 1968.

- Foreman, H., ed. 1970. *Nuclear power and the public*. [Based on a symposium held at the Univ. of Minn., October 10-11, 1969.] Minneapolis, Minn.: Univ. of Minn. Press.
- FRC. See Federal Radiation Council.
- FRC-NAS. See Federal Radiation Council-National Academy of Sciences.
- Friedell, H. 1983. *An overview of research in radiation biology and protective measures in the Manhattan Project during the war years, 1942-1946*. [Manuscript seen in draft form in 1983, courtesy of Dr. Friedell.]
- Gavankar, H. G. 1972. *Risks and emergency radiation doses from plutonium dioxide exposures*. Master of Science Thesis, June 1972. Univ. of Calif., Berkeley: Department of Nuclear Engineering.
- Gavankar, H. G., P. W. Durbin, and T. H. Pigford. 1974. *A basis for assessment of radiation risks for a hypothetical release of plutonium dioxide from a fast reactor accident*, CONF-740401, pt. 1, pp. 498-513. Paper presented at the American Nuclear Society topical meeting on fast breeder reactor safety, held in Beverly Hills, Calif., April 2-4, 1974.
- Gilbert, E. S. and S. Marks. 1979a. An analysis of the mortality of workers in a nuclear facility. *Radiat. Res.* 79:122-48.
- Gilbert, E. and S. Marks. 1979b. Comment on "Radiation exposures of Hanford workers dying from cancer and other causes." *Health Phys.* 37:791-92.
- Gilbert, E. S. and G. R. Petersen. 1985. A note on "Job related mortality risks of Hanford workers and their relation to cancer effects of measured doses of external radiation." *Br. J. Ind. Med.* 42: 137-39.
- Gofman, J. W. 1979. The question of radiation causation of cancer in Hanford workers. *Health Phys.* 37:617-39.
- Gofman, J. W. 1981a. *Radiation and human health*, pp. 214-19. San Francisco: Sierra Club Books.
- Gofman, J. W. 1981b. Response to the letter of P. Spiegler. *Health Phys.* 40:412-14.
- Hanford Environmental Health Foundation. 1983. *United States Transuranium Registry annual report, October 1, 1981 through September 30, 1982*. HEHF-38. Richland, Wash.
- Hanford Environmental Health Foundation. 1985. *United States Transuranium Registry annual report, October 1, 1983 through September 30, 1984*. HEHF-46. Richland, Wash.
- Harrison, G. E. and A. Sutton. 1967. Ratio of faecal to urinary clearance of strontium in man. In Lenihan, Loutit, and Martin 1967, pp. 161-66.
- Harrison, J. D. 1981. The gut uptake of actinides. *Radiological Protection Bulletin of the U.K.*, no. 41, pp. 14-19. United Kingdom: National Radiological Protection Board.
- Harrison, J. D., J. W. Stather, H. Smith, and G. N. Stradling. 1981. The influence of environmental factors on the gastrointestinal absorption of plutonium and americium. In *Actinides in man and animals*, ed. M. E. Wrenn, pp. 323-36. Proceedings of the Snowbird actinide workshop held in Snowbird, Utah, October 15-17, 1979. Salt Lake City: RD Press.
- Hawk, P. B., B. L. Oser, and W. H. Summerson. 1947. *Practical physiological chemistry*, 12th ed. Philadelphia, Pa.: The Blakeston Company.
- Hazle, A. J. 1982. State concerns for a uranium in drinking water standard. *Health Phys.* 43:91.
- Health Physics. 1960. Report of ICRP Committee II on permissible dose for internal radiation (1959). With bibliography for biological, mathematical and physical data. *Health Phys.*, vol. 3.
- HEHF. See Hanford Environmental Health Foundation.
- Heid, K. R. 1983. A comparison of systemic burdens at autopsy to estimates based on health physics data for selected plutonium workers. *Health Phys.* 44, Suppl. 1:477-83.
- Hempelmann, L. H., C. R. Richmond, and G. L. Voelz [with eleven individuals indicated as having participated in the work]. 1973. *A twenty-seven year study of selected Los Alamos plutonium workers*. LA-5148-MS. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Hempelmann, L. H., W. H. Langham, G. L. Voelz, and C. R. Richmond. 1974. Biomedical follow-up of the Manhattan Project plutonium workers. In *Proceedings of the 3d international congress of the International Radiation Protection Association*, ed. W. S. Snyder, CONF-730907-P1, pp. 713-18. Held in Washington, D.C., September 9-14, 1973. Oak Ridge, Tenn.: Technical Information Center.

- Hodge, H. C. 1973. A history of uranium poisoning (1824-1942). Chapter 1 in *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh, pp. 5-68. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.
- Hursh, J. B. 1972. *Basic radiation protection criteria* (NCRP Report no. 39). [Book review.]. *Health Phys.* 22:109-13.
- Hursh, J. B. 1975. Origin and basis of present standards for uranium. In *Conference on occupational health experience with uranium*, ERDA-93, pp. 25-34. Held in Arlington, Va., April 28-30, 1975. Washington, D.C.: Energy Research and Development Administration.
- Hursh, J. B. and N. L. Spoor. 1973. Data on man. Chapter 4 in *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh, pp. 197-239. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.
- Hutchison, G., B. B. MacMahon, S. Jablon, and C. E. Land. 1979. Review of report by Mancuso, Stewart, and Kneale of radiation exposure of Hanford workers. *Health Phys.* 37:207-20.
- ICRP. See International Commission on Radiological Protection.
- International Commission on Radiological Protection. 1951. ICRP supplement on maximum permissible amounts of radioisotopes. *Nucleonics* 8(2):70-75. [Also supplement to National Bureau of Standards Handbook 47, June 1951.]
- International Commission on Radiological Protection. 1955. *Recommendations of the ICRP*. Revised December 1, 1954. Section C. Report of Subcommittees I and II on permissible dose for internal radiation. *Br. J. Radiol.*, Suppl. 6, pp. 15-59. United Kingdom: British Institute of Radiology.
- International Commission on Radiological Protection. 1959. *Report of Committee II on permissible dose for internal radiation*, publ. 2. New York-London: Pergamon Press.
- International Commission on Radiological Protection. 1968. *Report on Committee IV on evaluation of radiation doses to body tissues from internal contamination due to occupational exposure*, publ. 10. New York-Oxford-London: Pergamon Press.
- International Commission on Radiological Protection. 1971. *The assessment of internal contamination from recurrent or prolonged uptakes*, publ. 10A. New York-Oxford-London: Pergamon Press.
- International Commission on Radiological Protection. 1972. *The metabolism of compounds of plutonium and other actinides*, publ. 19. Oxford-New York: Pergamon Press.
- International Commission on Radiological Protection. 1973. *Alkaline earth metabolism in adult man*, publ. 20. Oxford-New York: Pergamon Press. [Also *Health Phys.* 24:125-221.]
- International Commission on Radiological Protection. 1975. *Report of the task group on Reference Man*, publ. 23. Oxford-New York: Pergamon Press.
- International Commission on Radiological Protection. 1977. *Recommendations of the ICRP*, publ. 26. Annals of the ICRP, vol. 1, no. 3. Oxford-New York: Pergamon Press.
- International Commission on Radiological Protection. 1979. *Limits for intakes of radionuclides by workers*, publ. 30, pt. 1. Annals of the ICRP, vol. 2, no. 314. Oxford-New York: Pergamon Press.
- Kathren, R. L. and P. L. Ziemer, eds. 1980. *Health physics: A backward glance*. New York: Pergamon Press.
- Kneale, G. W. 1981. Stoll and Chakraborty's comments on "The question of radiation causation of cancer in Hanford workers" by John W. Gofman. *Health Phys.* 40:257-58.
- Kneale, G. W., T. F. Mancuso, and A. M. Stewart. 1981. Hanford radiation study III: A cohort study of the cancer risks from radiation to workers at Hanford (1944-77 deaths) by the method of regression models in life-tables. *Br. J. Ind. Med.* 38:156-66.
- Kneale, G. W., T. F. Mancuso, and A. M. Stewart. 1984. Job related mortality risks of Hanford workers and their relation to cancer effects of measured doses of external radiation. *Br. J. Ind. Med.* 41:9-14.

- Kneale, G. W., A. M. Stewart, and T. F. Mancuso. 1979a. Comments on "Review of report by Mancuso, Stewart, and Kneale of radiation exposure of Hanford workers", by G. B. Hutchison et al. *Health Phys.* 37:252-53.
- Kneale, G. W., A. M. Stewart, and T. F. Mancuso. 1979b. Radiation exposures of Hanford workers dying from cancer and other causes. *Health Phys.* 36:87.
- Krey, P. W., D. Bogen, and E. French. 1962. Plutonium in man and his environment. *Nature* 195:263-65.
- Langham, W. H. and J. W. Healy. 1973. Maximum permissible body burdens and concentrations of plutonium: Biological basis and history of development. Chapter 12 in *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh, pp. 569-92. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.
- Langham, W. H., S. H. Bassett, P. S. Harris, and R. E. Carter. 1950 and 1980. *Distribution and excretion of plutonium administered intravenously to man*. LA-1151. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory. Reprinted as a landmark paper in *Health Phys.* 38:1031-60.
- Larsen, R. P., R. D. Oldham, M. H. Bhattacharyya, E. S. Moretti, and D. J. Austin. 1981. On the gastrointestinal absorption of plutonium. In *Actinides in man and animals*, ed. M. E. Wrenn, pp. 303-7. Proceedings of the Snowbird actinide workshop held in Snowbird, Utah, October 15-17, 1979. Salt Lake City: RD Press.
- Lenihan, J. M. A., J. F. Loutit, and J. H. Martin, eds. 1967. *Strontium metabolism*. Proceedings of an international symposium held in Chapelcross, Glasgow and Strontian, Scotland, May 5-7, 1966. London-New York: Academic Press.
- Lloyd, E. 1967. A comparison of the metabolism of calcium and strontium in rabbit and man. In Lenihan, Loutit, and Martin 1967, pp. 167-73.
- Lundgren, D. L., R. O. McClellan, F. F. Hahn, G. J. Newton, and J. H. Diel. 1980. Repeated inhalation exposure of mice to $^{144}\text{CeO}_2$. I. Retention and dosimetry. *Radiat. Res.* 82:106-22.
- Mahaffey, J. A., C. L. Sanders, G. E. Dagle, and J. F. Park. 1981. A comparison of Pu metabolism and pulmonary tumors in dogs and rats exposed to $^{239}\text{PuO}_2$. In *Actinides in man and animals*, ed. M. E. Wrenn, pp. 541-55. Proceedings of the Snowbird actinide workshop held in Snowbird, Utah, October 15-17, 1979. Salt Lake City: RD Press.
- Mancuso, T. F., A. Stewart, and G. Kneale. 1977. Radiation exposures of Hanford workers dying from cancer and other causes. *Health Phys.* 33:369-85.
- Marks, S. 1975. A review of the Bell Study. In *Conference on occupational health experience with uranium*, ERDA-93, pp. 256-61. Held in Arlington, Va., April 28-30, 1975. Washington, D.C.: Energy Research and Development Administration.
- Marks, S. 1981. An introduction to the U.S. uranium registry. In *Actinides in man and animals*, ed. M. E. Wrenn, pp. 273-76. Proceedings of the Snowbird actinide workshop held in Snowbird, Utah, October 15-17, 1979. Salt Lake City: RD Press.
- Mays, C. W. and H. Spiess. 1984. Bone sarcomas in patients given radium-224. In *Radiation carcinogenesis: Epidemiology and biological significance*, eds. J. D. Boice, Jr. and J. F. Fraumeni, Jr., pp. 241-52. New York: Raven Press.
- McInroy, J. F., H. A. Boyd, B. C. Eutsler, and W. D. Moss. 1982. Plutonium concentrations in tissues of occupationally exposed nuclear workers. *Health Phys.* 43:124 (Abstract P/139). [Draft copy of full paper seen courtesy of Dr. McInroy.]
- Morgan, K. Z. 1945. *Tolerance concentration of radioactive substances*. Metallurgical Laboratory report CH-2801, with addendum, issued January 31, 1945, declassified April 12, 1954.
- Morgan, K. Z. 1946 and 1980. The responsibilities of health physics. *Scientific Monthly*, pp. 93-100. Reprinted as a landmark paper in *Health Phys.* 38:949-56.
- Morgan K. Z. 1947 and 1980. Tolerance concentration of radioactive substances. *J. Phys. Colloid Chem.* 51:984-1003. Reprinted as a landmark paper in *Health Phys.* 38:997-1014.
- Morgan, K. Z. 1967a. Letter dated July 13, 1967, to H. E. Stokinger at the Occupational Health Program, U.S. Public Health Service, Cincinnati, Ohio, concerning the work of the committee on threshold limits of uranium in air of the ACGIH. [From files of Oak Ridge National Laboratory by permission.]

- Morgan, K. Z. 1967b. *Radiation exposure of uranium miners*. Hearings before the Joint Committee on Atomic Energy, 90th Cong., Special subcommittee on research, development, and radiation, pt. 2, p. 1222. Washington, D.C.: U.S. Government Printing Office.
- Morgan, K. Z. 1972. Proper use of information on organ and body burdens of radioactive material. In *Assessment of radioactive contamination in man*, STI/PUB/290, pp. 3-23. Proceedings of a symposium held in Stockholm, November 22-26, 1971, Vienna: International Atomic Energy Agency.
- Morgan, K. Z. 1975. Suggested reduction of permissible exposure to plutonium and other transuranium elements. *Am. Ind. Hyg. Assoc. J.* 36:567-75.
- Morgan, K. Z., W. S. Snyder, and M. R. Ford. 1956. Maximum permissible concentration of radioisotopes in air and water for short period exposure. In *Proceedings of the international conference on the peaceful uses of atomic energy*, vol. 13, pp. 139-58. Held in Geneva, August 8-20, 1955. New York: United Nations.
- Morgan, K. Z., I. H. Tipton, and M. J. Cook. 1959. Summary of data used in revision of internal dose recommendations of the International Commission on Radiological Protection. In *Proceedings of the 2d United Nations international conference on the peaceful uses of atomic energy*, vol. 21, pp. 8-14. Held in Geneva, September 1-13, 1958. Geneva: United Nations. Also in *Progress in nuclear energy*, eds. W. G. Marley and K. Z. Morgan, vol. 1, pp. 17-28. New York: Pergamon Press.
- Morrow, P. E., L. J. Leach, F. A. Smith, R. M. Gelein, J. B. Scott, H. D. Beiter, F. J. Amato, J. J. Picano, C. L. Yuile, and T. G. Consler. 1982. *Metabolic fate and evaluation of injury in rats and dogs following exposure to the hydrolysis products of uranium hexafluoride*. NUREG/CR-2268. Washington, D.C.: Nuclear Regulatory Commission.
- NAS-NRC. See National Academy of Sciences-National Research Council.
- National Academy of Sciences-National Research Council. 1988. *Health risks of radon and other internally deposited alpha-emitters*. BEIR IV. Washington, D.C.: National Academy Press.
- National Bureau of Standards. 1941. *Safe handling of radioactive luminous compound*. NBS Handbook H-27. Washington, D.C.: U.S. Government Printing Office.
- National Council on Radiation Protection and Measurements. 1953. *Maximum permissible amounts of radioisotopes in the human body and maximum permissible concentrations in air and water*. [Issued as NBS Handbook 52, March 1953. Later numbered Report no. 11 of the NCRP, the first report of Subcommittee-2 on Internal Dose.]
- National Council on Radiation Protection and Measurements. 1959. *Maximum permissible body burdens and maximum permissible concentrations of radionuclides in air and in water for occupational exposure*. [Issued as NBS Handbook 69, June 5, 1959. Later numbered Report no. 22 of the NCRP. Addendum 1 was published in August 1963.]
- National Council on Radiation Protection and Measurements. 1985a. *General concepts for the dosimetry of internally deposited radionuclides*. Report of Scientific Committee-57 of the NCRP, Report no. 84.
- National Council on Radiation Protection and Measurements. 1985b. *Genetic risk from internal emitters*. Draft Report of Task Group of Scientific Committee-57 of the NCRP. [Published as *Genetic effects from internally deposited radionuclides*, NCRP report no. 89, August 1987.]
- NBS. See National Bureau of Standards.
- NCRP. See National Council on Radiation Protection and Measurements.
- Neuman, W. F. 1950. Urinary uranium as a measure of exposure hazard. *Ind. Med. Surg.* 19:185-91.
- Newton, C. E., Jr., H. V. Larson, K. R. Heid, I. C. Nelson, P. A. Fuqua, W. D. Norwood, S. Marks, and T. D. Mahoney. 1968. Tissue analysis for plutonium at autopsy. In *Diagnosis and treatment of deposited radionuclides*, eds. H. A. Kornberg and W. D. Norwood, pp. 460-68. Proceedings of the 7th annual Hanford biology symposium held in Richland, Wash., May 15-17, 1967. Amsterdam: Excerpta Medica Foundation.
- Newton, D., J. Rundo, and G. E. Harrison. 1977. The retention of alkaline earth elements in man, with special reference to barium. *Health Phys.* 33:45-53.

- Osborne, R. V. 1972. Permissible levels of tritium in man and the environment. *Radiat. Res.* 50:197-211.
- Parker, H. M. 1947 and 1980. *Health physics, instrumentation and radiation protection*. AEC report MDDC-783, declassified March 25, 1947. Reprinted as a landmark paper in *Health Phys.* 38:957-96.
- Parker, H. M. 1981. Protection programs of the plutonium project. Invited paper at the 25th annual meeting of the Health Physics Society. *Health Phys.* 41:571-76.
- Polednak, A. P. and E. L. Frome. 1981. Mortality among men employed between 1943 and 1947 at a uranium-processing plant. *J. Occup. Med.* 23:169-78.
- Raabe, O. G., S. A. Book, and N. J. Parks. 1980. Bone cancer from radium: Canine dose response explains data for mice and humans. *Science* 208:61-64.
- Raabe, O. G., N. J. Parks, and S. A. Book. 1981. Dose-response relationships for bone tumors in beagles exposed to ^{226}Ra and ^{90}Sr . *Health Phys.* 40:863-80.
- Ramsden, D., M. E. D. Bains, and D. C. Fraser. 1978. A case study of multiple low level exposure to plutonium oxide. *Health Phys.* 34:649-59.
- Rowland, R. E. and P. W. Durbin. 1976. Survival, causes of death, and estimated tissue doses in a group of human beings injected with plutonium. In *The health effects of plutonium and radium*, ed. W. S. S. Jee, pp. 329-42. Salt Lake City: The J. W. Press.
- Rowland, R. E., A. F. Stehney, and H. F. Lucas. 1983. Dose-response relationships for radium-induced bone sarcomas. In Rundo, Failla, and Schlenker 1983, pp. 15-31.
- Rundo, J. 1967. Kinetics of strontium-85 deposition in the skeleton during chronic exposure. In Lenihan, Loutit, and Martin 1967, pp. 131-38.
- Rundo, J. 1981. The late excretion of plutonium following acquisition of known amounts. In *Actinides in man and animals*, ed. M. E. Wrenn, pp. 253-60. Proceedings of the Snowbird actinide workshop held in Snowbird, Utah, October 15-17, 1979. Salt Lake City: RD Press.
- Rundo, J. 1983. Telephone communication, May 2, 1983.
- Rundo, J., P. Failla, and R. A. Schlenker, eds. 1983. Radiobiology of radium and the actinides in man. Proceedings of an international conference held in Lake Geneva, Wisc., October 11-16, 1981. *Health Phys.* 44, suppl. 1.
- Schulte, H. F. 1973. Memorandum to recipients of early version of report LA-4875, *Plutonium in autopsy tissue*. November 1, 1973.
- Scott, L. M., K. W. Bahler, A. De La Garza, and T. A. Lincoln. 1972. Mortality experience of uranium and nonuranium workers. *Health Phys.* 23:555-57.
- Serwer, D. P. 1976. *The rise of radiation protection: Science, medicine, and technology in society, 1896-1935*. (BEAC). [Informal report BNL-22279.] Upton, N.Y.: Brookhaven National Laboratory.
- Skrable, K. W., G. E. Chabot, and M. Johnson. 1981. Retention functions. In *Actinides in man and animals*, ed. M. E. Wrenn, pp. 559-606. Proceedings of the Snowbird actinide workshop held in Snowbird, Utah, October 15-17, 1979. Salt Lake City: RD Press.
- Snyder, W. S. 1967. Internal exposure. Chapter 10 in *Principles of radiation protection; a textbook of health physics*, eds. K. Z. Morgan and J. E. Turner, pp. 301-65. New York: John Wiley & Sons.
- Snyder, W. S. 1973. Internal exposure. Chapter 10 in *Principles of radiation protection; a textbook of health physics*, eds. K. Z. Morgan and J. E. Turner. Huntington, N.Y.: Robert E. Krieger Publishing Co. [Corrected and reprinted from original 1967 edition.]
- Spencer, H., I. Lewin, and J. Samachson. 1967. Influence of dietary and hormonal factors on radiostrontium metabolism in man. In Lenihan, Loutit, and Martin 1967, pp. 111-29.
- Spiegler, P. 1981. Comments on the question of radiation causation of cancer in Hanford workers, by J. W. Gofman. *Health Phys.* 40:411-12.
- Spieß, H. and C. W. Mays. 1973. Protraction effect on bone-sarcoma induction by ^{224}Ra in children and adults. In *Radionuclide carcinogenesis*, eds. C. L. Sanders, R. H. Busch, J. E. Ballou, and D. D. Mahlum, CONF-720505, pp. 437-50. Proceedings of the 12th annual Hanford biology symposium held in Richland, Wash., May 10-12, 1972. Springfield, Va.: National Technical Information Center.

- Spoor, N. L. and J. B. Hursh. 1973. Protection criteria. Chapter 5 in *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh, pp. 241-70. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.
- Stannard, J. N. 1970. Evaluation of health hazards to the public associated with nuclear power plant operations. In Foreman 1970, pp. 90-123.
- Stannard, J. N. 1975. The concepts of critical organ and radiation dose as applied to plutonium. *Health Phys.* 29:539-50.
- Stannard, J. N. 1981. Internal emitter research and standard setting. Invited paper at 25th annual meeting of the Health Physics Society. *Health Phys.* 41:703-8.
- Stannard, J. N. 1983. Some historical highlights and portents for the future of biomedical research on radium and the actinides. *Health Phys.* 44, suppl. 1:3-13.
- Stehney, A. F. A. P. Polednak, J. Rundo, A. M. Brues, H. F. Lucas, Jr., B. C. Patten, and R. E. Rowland. 1980. *Health status and body radioactivity of former thorium workers—interim report*. NUREG ICR-1420, ANL-80-30. Argonne, Ill.: Argonne National Laboratory.
- Stokinger, H. M. 1967. Letter to H. F. Schulte with copy to K. Z. Morgan, dated June 12, 1967. Commentary on the proposed increase in limit for uranium in air and enclosing a summary of proposed drinking-water standards. [From files of Oak Ridge National Laboratory, by permission.]
- Struxness, E. G., A. J. Luessenhop, S. R. Bernard, and J. C. Gallimore. 1956. The distribution and excretion of hexavalent uranium in man. In *Proceedings of the international conference on the peaceful uses of atomic energy*, vol. 10, pp. 186-96. Held in Geneva, August 8-20, 1955. New York: United Nations.
- Sullivan, M. F. 1980. Absorption of actinide elements from the gastrointestinal tract of rats, guinea pigs and dogs. *Health Phys.* 38:159-71.
- Sullivan, M. F. 1981. Actinide absorption from the gastrointestinal tract. In *Actinides in man and animals*, ed. M. E. Wrenn, pp. 311-22. Proceedings of the Snowbird actinide workshop held in Snowbird, Utah, October 15-17, 1979. Salt Lake City: RD Press.
- Tait, G. W. C. 1979. Comments on "Radiation exposures of Hanford workers dying from cancer and other causes" by T. F. Mancuso, Alice Stewart, and George Kneale. *Health Phys.* 37:251-52.
- Tanaka, G., H. Kawamura, and Y. Nakahara. 1979. Reference Japanese Man—I. Mass of organs and other characteristics of normal Japanese. *Health Phys.* 36:333-46.
- Tanaka, G., H. Kawamura, and E. Nomura. 1981. Reference Japanese Man—II. Distribution of strontium in the skeleton and in the mass of mineralized bone. *Health Phys.* 40:601-14.
- Task Group on Lung Dynamics. 1966. Deposition and retention models for internal dosimetry of the human respiratory tract. *Health Phys.* 12:173-207.
- Taylor, L. S. 1956a. Permissible exposure to ionization radiation. In *Proceedings of the international conference on the peaceful uses of atomic energy*, vol. 13, pp. 196-97. Held in Geneva, August 8-20, 1955. New York: United Nations.
- Taylor, L. S. 1956b. The achievement of radiation protection by legislative and other means. In *Proceedings of the international conference on the peaceful uses of atomic energy*, vol. 13, pp. 15-21. Held in Geneva, August 8-20, 1955. New York: United Nations.
- Taylor, L. S. 1971. *Radiation protection standards*. Cleveland, Ohio (now Boca Raton, Fla.): CRC Press.
- Taylor, L. S. 1979. *Organization for radiation protection*. The Operations of the ICRP and NCRP 1928-1974. COE/TIC-10124.
- Taylor, L. S. 1981. The development of radiation protection standards (1925-1940). *Health Phys.* 41:227-32.
- Taylor, L. S. 1984. The Tri-Partite Conferences on Radiation Protection. Canada, United Kingdom, United States (1949-1953). U.S. DOE report HVO-270 (DE 84016028). Washington, D.C.: U.S. Department of Energy, Office of Scientific and Technical Information.
- TGLD. See Task Group on Lung Dynamics.

- Thomas, R. H. 1983. The scientific basis of health and safety regulations. [Book review.] *Health Phys.* 44:89.
- Thompson, R. C. 1983. 1976 Hanford americium exposure incident. *Health Phys.* 45(4): 837-947.
- Tolley, H. D., S. Marks, J. A. Buchanan, and E. S. Gilbert. 1983. A further update of the analysis of mortality of workers in a nuclear facility. *Radiat. Res.* 95:211-13.
- United Nations Scientific Committee on the Effects of Atomic Radiation. 1977. *Ionizing radiation: Levels and effects. Vol. 1: Levels; Vol. 2: Effects.* United Nations Publication Sales Nos. E.72.IX.17 and E.72.IX.18. New York: United Nations.
- United Nations Scientific Committee on the Effects of Atomic Radiation. 1982. *Ionizing radiation: Sources and biological effects.* United Nations Publication Sales No. E.82.IX.8. New York: United Nations.
- UNSCEAR. See United Nations Scientific Committee on the Effects of Atomic Radiation.
- U.S. Congress. 1960a. *Radiation protection criteria and standards: Their basis and use.* Hearings before the Joint Committee on Atomic Energy, 86th Cong., Special Subcommittee on Radiation. Washington, D.C.: U.S. GPO.
- U.S. Congress. 1960b. *Selected materials on radiation protection criteria and standards: Their basis and use.* Hearings before the Joint Committee on Atomic Energy, 86th Cong., Special Subcommittee on Radiation. Washington, D.C.: U.S. GPO.
- U.S. Congress. 1963. *Fallout, radiation standards and countermeasures.* Hearings before the Joint Committee on Atomic Energy, 88th Cong., 1st sess., Subcommittee on Research, Development, and Radiation. Washington, D.C.: U.S. GPO.
- U.S. Congress. 1967. *Radiation exposure of uranium miners.* Hearings before the Joint Committee on Atomic Energy, 90th Cong., Subcommittee on Research, Development, and Radiation. Washington, D.C.: U.S. GPO.
- U.S. Congress. 1969. *Radiation standards for uranium mining.* Hearings before the Joint Committee on Atomic Energy, Subcommittee on Research, Development, and Radiation. Washington, D.C.: U.S. GPO.
- Voegtlin, C. and H. C. Hodge. 1953. Pharmacology and toxicology of uranium compounds. *National Nuclear Energy Series*, div. VI, vol. 1, pt. 3. New York: McGraw-Hill.
- Voelz, G., L. H. Hempelmann, J. N. P. Lawrence, and W. D. Moss. 1979a. A 32-year medical follow-up of Manhattan Project plutonium workers. *Health Phys.* 37:445-85.
- Voelz, G. L., J. H. Stebbings, Jr., J. W. Healy, and L. H. Hempelmann. 1979b. *Studies on health risks to persons exposed to plutonium.* LA-UR 79-3316. [Part of Conference for Radiation Accident Preparedness, October 19-20, 1979.] Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Voelz, G. L., J. H. Stebbings, L. H. Hempelmann, L. K. Haxton, and D. A. York. 1978. Studies on persons exposed to plutonium. In *Late biological effects of ionizing radiation*, STI/PUB/489, vol. 1, pp. 353-67. Proceedings of a symposium held in Vienna, March 13-17, 1978. [Also report LA-UR-78-208.] Vienna: International Atomic Energy Agency.
- Voelz, G., G. S. Wilkinson, J. W. Healy, J. F. McInroy, and G. L. Tietjen. 1983. Mortality study of Los Alamos workers with higher exposures to plutonium. In *Epidemiology applied to health physics*, CONF-830101, pp. 16-17. Proceedings of the 16th midyear topical symposium of the Health Physics Society held in Albuquerque, January 1983. Springfield, Va.: National Technical Information Service. [Note: More details on the workers were included in a refresher course that Dr. Voelz gave at the same meeting.]
- Wrenn, M. E. 1981. Discussion [after papers on uranium]. In *Actinides in man and animals*, ed. M. E. Wrenn, pp. 457-79. Proceedings of the Snowbird actinide workshop held in Snowbird, Utah, October 15-17, 1979. Salt Lake City: RD Press.
- Wrenn, M. E., R. L. Roswell, and P. W. Durbin. 1982. A model of uranium metabolism in humans and evaluation of risk from uranium exposure. Paper presented at the 27th annual meeting of the Health Physics Society held June 27-July 1, 1982. *Health Phys.* 43:89-90 (Abstract P/2).
- Wrenn, M. E., P. W. Durbin, B. Howard, J. Lipsztein, J. Rundo, E. T. Still, and D. L. Willis. 1985. Metabolism of ingested U and Ra. *Health Phys.* 48:601-33.

Preface to Section V Instrumentation

Instrumentation and methodology are sometimes described in the chapters already written and to follow, but only when they were key factors to the development under discussion.

Obviously, tremendous advances have been made in both since the days when some of the most basic measurements were made with relatively crude instruments. Progress in methodology is too specifically tied to the individual subjects under investigation to be reviewed as an entity. Those needing most to be described appear in connection with the research reviewed. However, integral to every experiment was the means to measure radioactivity in its various forms, and this needs an integrated discussion. The progression from simple electrometers to computerized and automated counting systems affected all aspects of the research reviewed in this book. Brief chronologies of the major steps in this progression are contained in the two chapters in this section.

Two major types of instrumentation can be identified. The first type applies primarily to the detection and measurement of radioactivity from radionuclides for purposes of monitoring plant operations or in the field. Many of the developments most identified with nuclear energy facilities of all kinds, including the many environmental measurements, were in this category. These instruments were, by and large, intended to be portable, rugged, easily operated, and versatile. Most of them met these criteria, although some of the sophisticated in-plant monitoring devices outgrew any reasonable definition of portability. Later developments in electronics and radiation detectors permitted a sharp reduction in size and weight of the truly field-type instruments.

The period of most rapid growth of these instruments occurred under the auspices of the Manhattan Engineer District (MED) during World War II. For security reasons, in part, and in part to add some color to what was sometimes a grim set of working conditions, many of these field and monitoring instruments were given code names that related either to what they did or what they looked like, but not to what their real purposes were. They were a governmental monopoly until the end of the war, when several private groups began manufacturing and improving these devices. It is no coincidence that these private groups were headed by individuals who had had much to do with the MED developments.

The second major type of instrumentation pertinent to the researches described in this book was used primarily in the laboratory. These were sensitive,

precise, and, especially in the middle years, heavy and bulky. An exception to the latter were the early electrometers and simple electroscopes and the photographic methods. Actually, sensitivity and precision were sufficient even with the early instruments to allow, for example, working out of the natural series of radionuclides (described in the preface to the first section of this book), as well as classic research. However, the devices available were difficult to set up and operate, and data accumulation was a slow process. The vacuum-tube amplifier changed all that, but the early instruments required much space, required considerable power, and had personalities of their own. A laboratory without a resident electronics expert was in deep trouble. Only with the development of solid-state circuitry and miniaturization has the laboratory instrument for measuring the radioactivity from radionuclides become reasonably compact and trouble free.

Precision designs of laboratory instruments began in 1928 in order to fulfill the requirements of the recently defined roentgen unit. In this area, the U.S. National Bureau of Standards was a leader in the development of the standard air ionization chamber as well as a center for calibration of field instruments. Laboratory instruments were under development throughout the 1930s for measurements of radioisotopes produced by accelerators. They underwent further development during the years of World War II, but not under the same conditions as the field and monitoring instruments. As the uses of radioactive tracers became commonplace, private instrument manufacturers supplied the needs of a great variety of laboratories, especially those for chemistry, biology, and medicine. To a degree, all of these, both specialized and routine, owed much of their development to the needs of and support from the Atomic Energy Commission.

In the decade of the seventies, and even more clearly in the decade of the eighties, the major developments in laboratory instrumentation have their roots in various aspects of nuclear medicine (chapter 20).

One important distinction between the two types of purpose and procedures is the degree of needed preparation of the sample. For the field and monitoring operations, measurements had to be made with the radionuclides in whatever form they existed. For the laboratory procedures, there were sometimes elaborate preparative steps, for example, to get a weak beta emitter or an alpha-particle emitter free from matrices such as body tissue, excreta, chemical compounds, etc., and thus reduce the interference with measurement that would otherwise occur. Frequently, these preparative steps took up more time and space than the radiation measuring steps. Typical examples are seen in chapter 12, figures 12.25 and 12.26, where the "mile of track" needed for preparing milk or separating noble gases for measurement is pictured. Another example, one for separating ^{14}C from biological compounds before measurement as CO_2 gas, is shown in figure PI-1.

Such preparative steps have become simpler with the development of liquid scintillation counting and other modern advances, but these came into general use relatively late in the decades covered by this book.

The field of instrumentation is special, and its history needs description by individuals who were closer to the developmental phases than was this author. Therefore, he enlisted help which was generously supplied by his former colleague and long-time friend, Dr. Howard L. Andrews (PHS, retired), formerly at the National Institutes of Health, Bethesda, Maryland, and later the University of Rochester, now residing in Jamestown, Rhode Island; and by another long-time

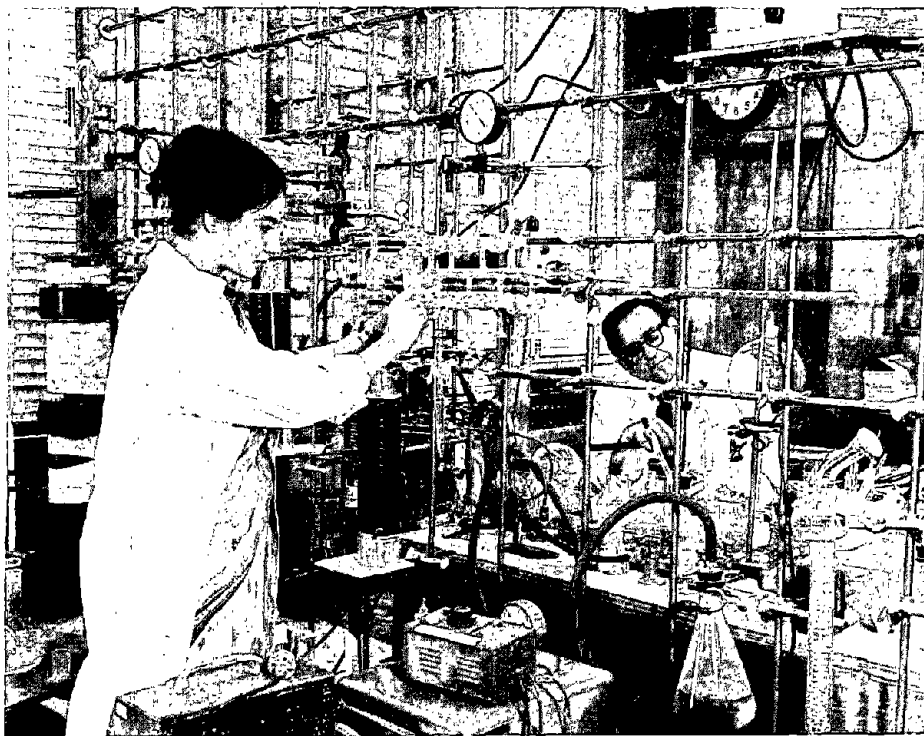


FIGURE PI-1. The "mile of track" needed to prepare biological materials for measurements of carbon-14 as $^{14}\text{CO}_2$ gas. In the background is Dr. Leon L. Miller, one of the developers of the method at the University of Rochester. (Photo courtesy of Dr. Irving Spar.)

friend and aficionado of the history of science, Ronald Kathren, now at Richland, Washington. Mr. Kathren has had broad experience in industry and contractor laboratories and has gathered an enviable collection of old to ancient radiation measuring instruments and literature concerning others, while Dr. Andrews has outfitted and managed several laboratories and field operations. I am greatly indebted to these two men.

Chapter 17, by Dr. Andrews, traces the development of instruments intended primarily for laboratory use. Chapter 18, by Mr. Kathren, considers the development of instruments for monitoring and field measurement of the radiations from radionuclides. Both emphasize developments in the United States because of the scope of the book, but no different principles are involved for instruments developed in any part of the world. Neither chapter dwells much on the preparative steps involved before measurement. The reader can find them well-documented in the original literature, which is copiously referenced in the pertinent chapters.

It should be clear from these chapters that development of instrumentation was continuous and significant throughout the years we are reviewing. The changes in recent years have added to convenience and speed more than to precision and sensitivity. Again, we must express admiration for what the early workers did with laborious and temperamental methodologies.

OUTLINE

LABORATORY MEASURING INSTRUMENTS

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Capsule Chronology^(a)

- 1895–1900** Photographic emulsions and electroscopes are the primary instruments used when radioactivity is discovered and the first radioactive elements isolated.
- 1900–1924** Gradual development of mechanical electrometers.
- 1911** Microscope used to count grain densities in photographic film.
- 1928** Roentgen unit accepted.
Description of basis for Geiger-Müller counter—soon called G-M tube.
- 1929** “Free air” ionization chambers used as primary standards.
Nuclear track photographic plates developed.
- 1930** Special vacuum tubes with high resistance and low current drain developed, e.g., the General Electric type FP-54.
Early count rate meter.
- 1930s** Much work on methods for producing quartz fibers for electrometers.
- 1933** DuBridge and Brown compensating circuit.
- Mid-1930s** Vacuum-tube electrometers gradually replace mechanical electrometers.
Work on quenching gases for G-M tubes.
- 1935** Eastman NTA plate in common use. Soon followed by NTB stripping emulsion.
- 1936–1960s** “Cavity chambers” used as secondary units for measuring ionization in a small volume of gas. Much work on composition of walls of such chambers. Victoreen “R-meter” is an early example.
- 1937** Lauritsen electroscope.
Extrapolation chamber of Failla.
- 1939** Binary scaler introduced as auxiliary pulse-counting equipment.
More useful count rate meter developed.
- 1940** Photomultiplier tube developed.
- 1940s** Enormous strides in ion chambers, vacuum tube electrometers, improved G-M tubes, pulse counting, discriminators, linear amplifiers, autoradiography, etc., taken under MED^(b) auspices.
- 1947** Higinbotham circuit.
Improved linear amplifiers.
Early pulse height analyzer.
Dynamic condenser electrometer (Palevsky, Swank, and Grenchik).

(a) The capsule chronology and summary and commentary were written by J. N. Stannard and were not reviewed by the chapter's author.

(b) For abbreviations and acronyms, see Appendix D.

1948 Halogen quenching gases introduced.

1950s The following were either introduced or improved significantly during the 1950s:

Vibrating reed electrometers.

Proportional counters.

Energy discriminators, pulse height analyzers.

Thallium-activated sodium iodide crystals.

Gamma-ray spectrometers.

Liquid-scintillation techniques.

Semiconductors.

Late 1950s Worldwide search for amber to use as electrical insulator in radiation measuring devices. Replaced later by synthetic plastics.

1960s Large crystals make whole-body counters able to measure many more radionuclides in the human body (Argonne, Los Alamos, and others).

Particle track-etching techniques developed.

1970s Thermoluminescence comes into wide use.

1980s Computer-assisted equipment expands greatly.

Chapter 17

Laboratory Measuring Instruments

by Howard L. Andrews, Scientist Director U.S. Public Health Service (Ret.) and former Professor of Radiation Biology and Biophysics, University of Rochester School of Medicine and Dentistry.

I. The Pioneer Years, 1895 to 1940

A. In the Beginning

Sensitive instruments and measuring techniques were immediately available for application to the pioneering discoveries of Roentgen and Becquerel. The initial detection of x rays late in 1895 and the beta particles from radioactive decay three months later were made with photographic emulsions. Electroscopes using thin gold foils as the sensing element were in use at the time of the original discoveries and quickly demonstrated the ionizing capabilities of the newly discovered radiations.

The use of photographic emulsions has continued and for particular purposes they provide unique information, but techniques based directly on the electrical detection of ionization have borne the main burden of radiation measurements.

Electrometers of many designs soon supplemented the simple electroscopes. The distinction between the two is subtle and need not concern us here. Madame Curie used the "electric method" in her early studies, including those that led to the determination of the activity of a weighed sample of radium, from which the decay constant and the half-life could be calculated.

B. Moving-Element Electrometers

The ions produced in a closed chamber by a single alpha particle could be barely detected by the most sensitive electrometers. These instruments utilized the movement of a thin foil, a fine (about $0.5\text{-}\mu\text{m}$) quartz fiber, or a moving vane suspended by a fine fiber. The position of the moving element was determined by a microscope or with a lamp, mirror, and scale.

Mechanical electrometers are sensitive but temperamental detectors of electric charge or potential, depending upon the circuit arrangement. Ion currents can be measured from the rate of movement of the sensing element or by its

steady deflection when the current flows through a high resistance (10^7 to 10^{10} ohms).

Mechanical electrometers are very difficult to set up and adjust to optimum working conditions. As the sensitivity is increased, the moving element tends to become unstable, eventually responding to internal conditions rather than to external signals. Fluctuations in the Brownian movements of the gas molecules in the instrument case produce a fluctuating zero position. Electrometers are necessarily enclosed in metal to protect against air currents and to provide electrostatic shielding. Massive copper shielding is usually added to reduce thermal gradients, and an elaborate vibration-damping mount is usually required.

At high sensitivities, the response time of an electrometer is very long, although it can be reduced somewhat by a partial evacuation of the case—another complication. A single rate-of-charge measurement may require an hour or more. The results obtained with these instruments are a tribute to the patience and the experimental skills of the early workers.

The designs of Hoffman in 1912 and of Lindemann in 1924 probably represent the ultimate in mechanical electrometers. Although some of these instruments were in use well into the 1940s, they were then being replaced with vacuum-tube electrometers. From then on, they played no role in the rapidly developing field of radiation.

Although it lacked the ultimate sensitivity of some other designs, the Lauritsen electroscope (Lauritsen and Lauritsen 1937) deserves special mention. The sensing element consists of a simple T-shaped quartz fiber about $5\text{ }\mu\text{m}$ in diameter, made conducting with a thin film of gold and mounted directly in an ionization chamber. The position of the fiber is read with a microscope and an eyepiece scale. An electric charge (which could be produced by rubbing a pocket comb on some wool) placed on the system deflects the fiber from its zero position. Ions produced in the chamber neutralize some of the charge and the fiber returns toward its zero position at a rate that depends upon the rate of ionization.

A versatile laboratory instrument, the Lauritsen design was also rugged enough for field use. These electroscopes were used by the Japanese at Hiroshima to give the first indication that ionizing radiation had accompanied the detonation. They were in use as late as the 1950s in some studies in radiobiology but were then being replaced by vacuum-tube electrometers. Pocket dosimeters, widely used today in personnel monitoring, are adaptations of the Lauritsen design.

C. Ionization Chambers

In principle, an ionization chamber consists of an enclosed gas volume with two collecting electrodes, one of which is highly insulated and is connected to an electrometer. In practice, certain special shapes, sizes, and constructions are best suited to specific purposes.

In 1928, the roentgen (r) was accepted by the International Commission on Radiological Units (ICRU) as the unit of radiation dose (Taylor 1958). Based on the number of ions produced in air, the strict fulfillment of the definition requires an instrument in which all of the ions collected do indeed originate in air. These "free-air" chambers (Taylor 1929) are suitable for use only in standardizing laboratories, such as the National Bureau of Standards (NBS), where they have been available for the calibration of secondary standards. Over

limited energy ranges, these secondary standards may closely approximate the response of a true air chamber.

Much theoretical and experimental work has been done over an extended period of time on these secondary or "cavity chambers" (Gray 1936; NBS 1961). In a cavity chamber, the measured ionization is produced in a small gas volume (usually air) enclosed within solid walls. The composition of the walls can be made essentially "air-equivalent" or "tissue-equivalent" as required, and the wall thickness chosen to be compatible with the ranges (energies) of the ions to be collected. One of the earliest instruments of the cavity-chamber type is the r-meter manufactured by the Victoreen Instrument Company. The r-meter is essentially a string electrometer with removable cavity chambers of various volumes and wall thicknesses. The original Victoreen design was based on the earlier work of Fricke and Glasser (1925) and on that of Glasser, Portmann, and Seitz (1928). With only minor modifications, the r-meter is in extensive use today.

The "extrapolation chamber" developed by Failla (1937) was designed to permit dose determinations in a tissue having a uniform concentration of a radioisotope. It also serves to measure the dose due to a beta emitter located at or just below the surface of the skin. The extrapolation chamber consists of a parallel-plate ion chamber with an adjustable ion-collecting space between the electrodes. A series of measurements taken at various collecting volumes can be extrapolated to zero volume to give the dose independent of the disturbing effect of the chamber itself.

D. Materials of Construction

Specially selected materials were required for the construction of ionization chambers and electrometers, and this holds true for the more sophisticated instruments in use today. Improvements in instrument performance have come more from design refinements and the use of new and improved components than from the use of new fundamental principles upon which the measurements are based.

From the time of the earliest electroscope to the present, electrical insulators have been particularly critical components. Natural amber and crystalline quartz were quickly recognized as superior insulators. Cast rhombic sulphur was found to be suitable for some less critical applications and was much cheaper. Amber was particularly useful because it can be machined easily into useful shapes. In the late 1950s, a worldwide search was undertaken to procure as much of this critical material as possible. Later, the development of synthetic plastics relieved the pressure on scarce amber and quartz, and eventually insulators with superior qualities were produced. In particular, some synthetic materials show a greater stability at high radiation doses and less "soak-in," a process where charges migrate in and out of the insulator.

For many years, the multimegohm resistors were made by drawing lines with a graphite pencil or with drawing ink on a cardboard or celluloid backing. The resistance values obtained were largely a matter of chance and were subject to undesirable changes with temperature and humidity. During the 1940s, stable ceramic resistors were developed by the S. S. White Dental Manufacturing Company, and soon other companies were offering comparable items.

Prior to the enormous instrument requirements of the Manhattan Engineer District (MED), much of the early equipment was made by the users. *Procedures in Experimental Physics* (Strong 1947), a classic text first published in 1938,

devoted one chapter to methods of producing the fine quartz fibers needed for electrometers. Another chapter described methods for depositing electrically conducting films on the fibers. Still another chapter gave detailed instructions for the manufacture of Geiger-Müller (G-M) tubes.

One of the lost spectacles of the early physics laboratories is the production of quartz electrometer fibers by the cross-bow method. A bow and arrow were set up at the end of a long corridor with the arrow restrained by a short piece of quartz rod. When the quartz was suddenly melted with an oxy-hydrogen flame, the released arrow generated a fine fiber, which was to be found by a hands-and-knees search on the floor, previously covered with black cloths.

As laboratory measurements became more reliable and sensitive, it became evident that low levels of naturally occurring radioactive isotopes are present in many materials. Unless all structural components are carefully chosen, the instrument itself may contribute more activity than the sample being assayed. One of the first applications of the vacuum-tube electrometer was to a detailed investigation of materials of interest in instrument construction (Bearden 1933).

E. Radiation Sources and Applications

Before the release of classified information from the MED, there were relatively few sources of radiation and few applications. Instrumentation was correspondingly limited. Patients were being treated with "soft" x rays (30 to 100 kVp) for superficial lesions, and "deep therapy" at 250 kVp was used for deep-lying tumors. Engineering developments were slowly pushing the "hard" x-ray voltages upward to 2 MeV during the 1930s and 1940s.

Some organ tumors were treated by implanting radon "seeds" utilizing radon gas pumped off from a solution of ^{226}Ra . A large hospital with an active cancer service might have a radon plant consisting of a 100- to 1,000-mCi solution of radium bromide. The plant operator used a hand-operated mercury pump to force the gas liberated by radium decay into fine glass or gold capillary tubing. This tubing was then sealed off into a series of seeds, each calculated to have the activity specified by the radiologist for the case in hand.

After sealing, each seed was checked by comparing its activity to that of a standard source. The usual arrangement consisted of an ion chamber-electrometer setup with carefully controlled source and chamber positions. The NBS developed some standards to which the seeds could be compared. Curtiss et al. (1940) reported on plans of the Bureau to provide radium samples containing either 10^{-9} or 10^{-11} grams of ^{226}Ra in 100 ml of solution, sealed ampoules of thorium, and standard samples of radioactive rock.

Industrial applications of radioactive materials were limited largely to their use in self-luminous paints. Many of these preparations were crude mixtures of a variety of naturally occurring radioisotopes. Few activity measurements were made, and in many cases the composition of the mixture was unknown. These uncertainties introduced serious difficulties when attempts were made to deduce allowable exposure limits from the injuries observed in the New Jersey dial painters.

F. Manmade Radioisotopes^(a)

The early 1930s were years of great scientific productivity. Chadwick reported the identification of the neutron in 1930. Joliot and Curie produced artificially

(a) [See also chapter 5.]

induced radioactivity in 1934 utilizing the alpha particles from naturally occurring isotopes. The era of high-energy particle accelerators opened when Lawrence and Livingston (1932) described the design and performance of the first magnetic resonance machine, named the cyclotron. This was quickly followed by the development of the electrostatic accelerator (Van de Graaff, Compton, and Van Atta 1933). No longer was man restricted to the naturally occurring radioisotopes; he could now make his own. Uses now expanded rapidly, and this stimulated the development of equipment for the quick and accurate assay of a rapidly increasing number of isotopes.

In spite of the increased production and use, there were some uncertainties as to just what was being measured. During 1938 and 1939, a series of papers in *Physical Review* discussed the possibility that the beta particles emitted by radioactive nuclei had a variety of masses instead of being strictly identified with the negative electron. Some thought that energy considerations required slow-speed betas to have a greater rest mass than those of higher energy (Jauncey 1938). The theoretical studies of Pauli and the acceptance of the existence of the neutrino settled the controversy in favor of a single beta particle rest mass.

G. Vacuum-Tube Electrometers

Vacuum tubes, applied enthusiastically to the field of communications, seemed to offer important advantages over mechanical electrometers. During the 1920s, astronomers had been attempting to use vacuum tubes as electrometers to measure the minute electric currents produced in photoelectric cells coupled to their telescopes. The problems that they encountered were similar to those involved in ion-current measurements. Only partial success was achieved with the types of tubes that were being used successfully in communications, where performance demands were less severe.

Eventually, special attention was given to the critical parameters in tube design, and some tubes with remarkable characteristics were developed. Elaborate steps were taken to obtain the highest possible vacuum, and, to eliminate ionization in any residual gas, the tubes were operated at only 4 to 6 V, well below any ionization potentials. Internal mounts and external leads were designed to have the greatest possible resistance to leakage currents. Victoreen, Western Electric, Westinghouse, and General Electric each produced electrometer tubes, with the General Electric type FP-54 the most outstanding (Metcalf and Thompson 1930). Ion currents of 10^{-17} A or even less could now be measured routinely and rapidly.

Compensating circuits (DuBridge and Brown 1933) were developed to minimize disturbances due to changes in battery voltages and to fluctuations in filament emission. Ion current measurements could now be obtained from a rugged galvanometer or microammeter in the plate circuit of the electrometer tube. The hypercritical high-resistance, low-leakage circuit was now limited to the ion chamber itself and to the grid of the electrometer tube.

Although the vacuum tube brought its own particular problems, the critical mounting and shielding required with the mechanical electrometers was eliminated. The time required to make a measurement was sharply reduced. During the exploratory phase of any technique, one is gratified for any measurement, however much effort is required to make it. In moving into exploitation, speed and ease of measurement become important. The introduction of the vacuum tube into ionization measurements not only shortened assay times but also

permitted measurements by personnel who would have had great difficulties with the mechanical electrometers.

H. Pulse Counters

When the ion-collecting voltage across an ion chamber is increased, primary ions generated by the radiation may acquire enough energy to produce secondaries by collision. These secondaries add to the primaries to produce a pulse of ionization 10^2 to 10^9 times as large as that from the primaries alone, the amount of amplification increasing with increasing voltage. An assay now consists of counting the number of pulses rather than measuring the total primary ionization produced by some initiating event.

By 1908, Rutherford and Geiger were making use of secondary, or avalanche ionization, using the Geiger point counter to detect alpha particles. Later, the needle point was replaced by a fine wire (about 0.1-mm diameter) stretched along the axis of a cylindrical cathode (Geiger and Müller 1928). These devices were the ancestors of the modern proportional and G-M counter tubes.

At atmospheric pressure, useful values of amplification require stable sources of 1,000 to 5,000 V, values not readily attainable with the early (or modern) batteries. Full exploitation of gas amplification awaited the development of highly stabilized sources of high voltage made possible with vacuum tubes.

At gas amplification factors of 10^2 to 10^3 , the size of the avalanche pulse is strictly proportional to the number of primary ions formed by the radiation. These pulses may still be too small for direct recording, but vacuum-tube linear amplifiers were designed to raise the signal level while still maintaining proportionality. Because of the overall proportionality of the system, such a counter can readily discriminate between the massive localized ionization of an alpha particle and the sparse ionization of a beta.

When the gas pressure in a pulse-counter tube is reduced to perhaps 10 cm of mercury, gas amplification factors of 10^7 to 10^8 may be obtained with voltages of less than 1,000. The ultimate sensitivity has been attained because a single ion pair is now capable of initiating an ion pulse up to the full capability of the tube. A massive primary ionization can do no more, and the tube has lost its ability to discriminate between different sizes of primary events.

I. Making G-M Tubes

In the decade following the Geiger-Müller paper of 1928, a spate of papers appeared on various aspects of G-M tube manufacture. An intense interest in pulse counting was generated by the controversy over the nature and origin of cosmic rays, in which Nobel laureates Compton and Millikan were the chief antagonists.

The basic principles involved in pulse counting were only gradually discovered during this period, and many of the early papers were in the nature of cookbook recipes. Some tubes were fast, with pulses of 10^{-5} -sec duration; others were slow, with 0.1-sec pulses, and there were many failures.

One of the earliest problems involved the tendency of the G-M tube to respond to a single ionizing event with a series of repetitive pulses. This tendency toward continuous discharge could be suppressed by adding a high resistance, but the response time of the tube then became very long. A variety of vacuum tube circuits (Neher and Pickering 1938) were devised to stop, or quench the discharge and ready the tube for another without lengthening the response time.

A wide variety of counting gases were studied, leading to the choice of argon for most applications, a choice still valid today. Many gas mixtures were tried, and Trost (1937) reported that the addition of some 10% of certain complex molecules to the basic counting gas would suppress the tendency to go into continuous discharge. This finding was vigorously pursued, and quickly self-quenching tubes containing some organic molecule such as ethanol or xylene were in common use. Some of the organic quenching gas is used up in each discharge so these tubes have a finite counting life, and, in addition, their efficiency is somewhat temperature dependent. In spite of these drawbacks, the old non-self-quenching tubes were quickly outmoded for most applications.

As the G-M tube became more reliable, it was applied to a variety of assays of interest in biology and radiochemistry. On the one hand, thin "windows" were developed to improve the entrance of low-energy beta particles into the sensitive volume. On the other hand, some tubes were made with unusually heavy cathodes to enhance the absorption of gamma-ray photons, which were then detected through the liberated electrons.

One of the unusual applications was the use of G-M tubes (Evans 1937) to measure the radium content in living persons, the first human whole-body counter.

J. Auxiliary Pulse Counting Equipment

The avalanche discharge in a G-M tube is sufficient to produce a detectable deflection in a string electrometer, but the response time of the string is very long compared to the pulse duration, and so the full counting capability of the tube cannot be realized. High-speed pulse counting followed the introduction of scaling circuits. These devices were typically based on a binary or scale-of-two vacuum-tube circuit, which passed along one pulse for every two incident upon it. A series of these circuits reduces the number of input pulses by factors of 2, 4, 8 . . . 2^n . Many variants of the basic binary scaler were introduced during the 1930s (Lifschutz 1939).

With a sufficiently high scaling factor, the number of output pulses can be recorded on a mechanical counter. In the 1930 era, the choices in these counters was limited, and none had been designed to be driven efficiently by a vacuum tube. Central Scientific Company offered a slow register that required a large amount of power. A limited number of message registers were available from Western Electric, and later Cyclotron Specialties designed a counter more suited to vacuum-tube operation. None of these mechanical devices was entirely satisfactory.

With a scaling circuit, the total pulse count over some determined time required multiplying the reading of the mechanical register by the scaling factor, and then adding the number of pulses that were in the scaling system but which had not yet activated the register. Symbolically:

$$\text{Pulse count} = \text{Register} \times \text{Scaling factor} + \text{Interpolation}$$

The chance for an error in making this calculation for every assay is substantial, in spite of help from various devices designed to facilitate the process.

K. Count-Rate Meters

When a count rate of one hundred or more a minute is available, the pulses can be electronically averaged over some convenient time interval and the average

displayed on a deflection-type meter. Rate meters are particularly useful for studying the decay of radioisotopes because the meter can be connected to a chart recorder to provide a continuous record of the activity. One of the earliest rate meters was described by F. V. Hunt in 1930. Various design improvements followed, and by the end of the decade, sophisticated rate meters incorporating many of the features in use today were available (Evans and Alder 1939). The rate meter is one example of an instrument whose development came from the demands of biology and chemistry rather than from cosmic-ray research.

L. Photographic Emulsions

The first evidence for the existence of ionizing radiations came from the general blackening of photographic emulsions and from the shadows cast on them by strong absorbers of the radiations. It was quickly discovered that each of the three types of radiation (alpha, beta, and gamma) could produce an effect on photographic materials. However, electric methods of ionization measurements became preferred for accurate quantitation. In 1935, Compton and Allison would state, "Though it is usually employed to give only qualitative results, the photographic plate can also be adapted to precise quantitative comparisons of x-ray intensities." (Compton and Allison 1935)

Film blackening was quickly exploited by physicians for the x-ray examination of deep-lying body structures. This application required fine-grained emulsions of high sensitivity to photons. The market demands were large, and improvements by film manufacturers led to finer detail in the shadow pictures with a reduced radiation exposure of the patient.

Some attempts were made to use films for measuring the exposure of radiation workers, but most of these were of dubious value because of the lack of controlled conditions of exposure, processing, and evaluation. In one laboratory, a worker's exposure was considered acceptable if a newspaper could be read through a film of unspecified sensitivity, processed in casual, uncontrolled fashion.

Discrete tracks produced by individual alpha particles were observed very early, and, by 1911 microscopic examination of the developed emulsions were being made to determine grain densities along the tracks.

The chief push for better particle track counting came from the physical rather than from the biological sciences. Cosmic-ray investigators required unusually thick emulsions in order to record reasonable portions of the tracks of high-energy particles. Ilford, Agfa, and Eastman each were producing special nuclear track plates by the late 1920s. By 1935, the Eastman NTA plate was in common use, and the NTB stripping emulsion quickly followed. The emphasis was still on physical applications. A comprehensive review (Shapiro 1941) made no mention of uses of nuclear track plates in biology, although there had been some limited applications many years before (Lacassagne and Lattès 1924).

II. From Eclipse to Declassification

A. Transition

A few pioneering biological tracer studies had been done in the 1930s, utilizing ^{210}Pb obtained from used radon seeds whose gamma-ray activity had dropped below useful therapeutic levels. Many other elements were of greater biological interest, and these only awaited availability to be rapidly exploited. With the

discovery of artificial radioactivity and the construction of high-energy particle accelerators, many new radioisotopes became available in useful quantities.^(a)

The late 1930s saw sharply increased interest in radiation and the use of radioactive isotopes. There was a corresponding increase in the number of papers published on the related instrumentation. Then the decision was taken to proceed with research on the possibility of producing nuclear weapons. The MED was created, and General Leslie Groves was appointed director in mid-1942, to remain until December 31, 1946.

The magnitude of the task ahead was appreciated early, and a large number of those who had been working with radiation were recruited into the project. Physical scientists were needed to develop methods for producing the parent materials and for fashioning them into an energy-releasing structure. Biological scientists were needed to investigate pharmacological properties of a host of new, manmade elements and of others previously known only as laboratory curiosities.^(b) All scientific results originating within the project were classified and barred from free publication.

The number of papers published on all phases of radiation research dropped sharply. Previously, most of the papers on instruments and techniques had been published in *Review of Scientific Instruments*. A cursory survey of the record of this journal shows the effect of the MED recruitment:

Number of Papers in *Review of Scientific Instruments* Related to Radiation Measurements

1940 — 15	1946 — 18
1941 — 12	1947 — 37
1942 — 6	1948 — 50
1943 — 7	1949 — 42
1944 — 1	1950 — 34
1945 — 3	

These data should have been of more than passing interest to our opponents in World War II.

B. The Organization

Faced with an enormous and perhaps impossible task, the MED decided to push concurrently several promising lines of research. A series of laboratories was set up at Berkeley, Chicago, Los Alamos, Oak Ridge, and Rochester, to name only a few. Each laboratory had a specific task, such as production, purification, weapons design, or biological effects. Each had specific instrument requirements, although there were areas of overlap and some common problems. Each had an instrument group in partial, but frequently incomplete, communication with the others.

(a) [See also chapter 5.]

(b) [Details in chapters 6 and 7.]

At the start of the project, each group had available the instrument types described in section I of this chapter. In addition, each had some relatively primitive instruments for neutron measurements. Discussion of these instruments has been omitted here, because only under the most unusual conditions will neutrons arise from emitters internal to the body.

C. The Instrumentation Task

Formidable problems faced the instrumentation groups. The fission process would produce large numbers of hitherto unknown isotopes whose individual radiations had to be determined. Separation and purification procedures would require instruments to properly identify and quantitate the individual components. Alpha-particle assays, frequently in the presence of high beta activity, would become of paramount importance in the production of fissionable materials and in studies of their biological fates. Before the creation of the MED, radioactive materials had been relatively scarce, and instrument developments had emphasized the assays of small, submicrocurie quantities. These assays would still be needed, but, in addition, multimicrocurie activities were expected, and instruments had to be devised to cope with them.

Developments proceeded on all types of instruments. Ion chambers and vacuum-tube electrometers were needed in many applications. The production of improved G-M tubes was expanded, and new designs of auxiliary pulse counting equipment were made. Upper and lower energy discriminators were added to linear amplifiers to permit the counting of only a limited energy range, an aid in identification and in the reduction of background counts. Photographic techniques (autoradiography), using either special nuclear-track or conventional emulsions, were developed to study the distributions in tissues of the many newly available radioisotopes (Axelrod and Hamilton 1948).

Radiation safety formed an important part of the MED program, and again new instruments and techniques were needed. Assay methods for all kinds of emitters had to be devised, utilizing air and breath samples, urine and fecal specimens, and surface wipes. In most cases, the assays required both identification and quantitation.

Throughout the program, some very grave value judgments had to be made. Instrument improvements tend to become a continuous process as new materials, components, and ideas are fed into the research and development system. Under great time pressure, when must development be frozen and manufacture start, perhaps to produce an instrument that is partly obsolete by the time it is in use? It is a tribute to all concerned in the MED that the instruments and techniques that were developed, while perhaps not always ideal, were adequate for the job at hand.

D. Declassification

At the conclusion of World War II, the decision was taken to publish all of the findings of the MED that did not jeopardize national security. Declassification proceeded rapidly, considering the enormity of the task and the irreversible nature of the releases.

Much of the declassified material was published by McGraw-Hill in the National Nuclear Energy Series. The project activities were divided into eight divisions:

- I. Electromagnetic Separation Project
- II. Gaseous Diffusion Project
- III. Special Separation Project
- IV. Plutonium Project
- V. Los Alamos Project
- VI. University of Rochester Project
- VII. Materials Procurement Project
- VIII. Manhattan Project

Division V, Volume 2, *Ionization Chambers and Counters*, written by B. B. Rossi and H. H. Staub (1949) is of the most present interest. One of the authors' aims was to show "how we did it," and to some extent the volume today has something of a cookbook flavor—not so when it was published. It was evident that the MED had added enormously to the basic knowledge behind the practical design of radiation measuring instruments.

Individual scientific papers were also published on many parts of the instrument program. Only a few can be mentioned here. Higinbotham, Gallager, and Sands (1947) published the detailed design of a binary scaler that was to be a standard of performance for several years. Similarly, Jordan and Bell (1947) developed a vastly improved linear amplifier for use in proportional counting. The alpha-proportional counter of Simpson (1947) provided efficient counting of alpha particles with a high rejection rate for betas.

In spite of the remarkable progress made during the project, instrument development was by no means complete, and this situation will continue as long as radiation measurements are made. However, postproject developments started from a much higher quantum level than existed initially.

III. After the MED

A. The Takeoff

The use of radiation and radioactive materials expanded explosively following the declassification of MED information. High-voltage accelerators of several kinds were designed and built. Some of these produced very penetrating x-ray beams used in the treatment of deep-lying tumors and in commercial applications. Others produced radioisotopes for a proliferating demand.

Both the number of isotopes and the quantities available increased dramatically in 1948 with the release of products from the reactor at Oak Ridge National Laboratory. Carbon-14 and hydrogen-3 (tritium) were of particular importance in biology and medicine, but their relatively low-energy beta emissions posed some measurement problems.

Radiochemical companies began to take over the sometimes difficult job of incorporating radioactive atoms at specific locations in complex molecules. A large number of labeled compounds became almost stock items, in microcurie quantities for tracer studies and in millicuries for the controlled destruction of unwanted biological tissues. Multicurie sources were used for the inspection of metals for hidden flaws and for a variety of irradiations. In one large medical institution, the amount of radioactivity utilized increased exponentially for over fifteen years, with a doubling time of about three years.

Regulations designed to ensure the radiation safety of workers, patients, and the general public were developed and promulgated. Proofs of personnel competence and adequate facilities were required to obtain materials from the

Atomic Energy Commission, successor to the MED. Building on the safety requirements developed by the MED, instruments were now required for radiation safety measurements as well as for the assays of primary interest. Field samples were brought to the laboratory for analysis, and bioassays of breath, urine, or other biologicals served to determine the body burden of internal emitters. In these measurements, the identification of the emitters was as important as the activity. The Health Physics Society, organized in 1955, continues to foster the development and application of practices that will ensure the safe uses of radiation.

Pressures on instrument manufacturers came from several directions. Reliability was, of course, of paramount importance. Increased response to low activities was demanded in order to reduce assay times and to permit the use of smaller amounts of active materials.

It is axiomatic that only those ionizations that occur within the sensitive volume of the detector will be recorded. Some of the most important of the newly available isotopes emit only low-energy radiations, and special techniques and equipment were needed to assay them efficiently. Methods had to be devised to permit the reproducible measurement of samples that could be put directly into the sensitive detector volume without disturbing its basic characteristics. Ultra-thin "windows" were needed to reduce losses by absorption from samples external to the detector. Geometrical relations between the sample and the detector had to be arranged so that the latter would intercept as many of the emitted radiations as possible, while maintaining constant conditions of radiation scatter from the counting equipment. Counting "geometry" had to be high and strictly reproducible. Obviously, development in technique had to go hand-in-hand with the improved instrumentation.

A host of instrument manufacturers came into being during the early post-MED period. Competition was keen. Some companies foundered on technical inadequacies, others grew so rapidly that control passed from engineering to business management, apparently a necessity for large-scale survival.

B. Ionization Chambers

Ion chambers used in the laboratory are designed to measure activities in curies rather than exposures in roentgens, and so they are free from the constraints imposed on the design of an air-equivalent chamber (see section I C of this chapter). Then the size and shape of the chamber can be chosen to fit the particular job at hand.

Spherical chambers can be used when the size of the sample approximates a point source. Cylindrical chambers are more common primarily because of the ease of manufacture. In a cylindrical chamber, the sample can be mounted at one end of the sensitive volume so that essentially 50% of the emitted radiations enter the chamber (2π geometry). When mounted on a very thin film at the center of a cylindrical chamber, a sample can be assayed with nearly 100% or 4π geometry. In either case, the chamber dimensions are so chosen that all of the ionizations take place in the gas and not in the chamber walls.

In many assays, thin film mounts are required in order to obtain a high and reproducible counting geometry. Thin films reduce uncertainties due to back-scattered particles from the mount; they also reduce energy losses by absorption.

Since charged particle absorption is a function of specific mass, it is customary to rate films in equivalent thickness, usually $\mu\text{g}/\text{cm}^2$. For reasons of strength,

films of plastics such as formvar, nylon, and mylar replaced metals such as aluminum or thin sheets of mica. Films of $10 \mu\text{g}/\text{cm}^2$ can be made routinely, and thinner ones are possible (Yaffe 1962).

Although most ion chamber measurements are made at or slightly above atmospheric pressure, high-pressure chambers are sometimes used to increase ion absorption and reduce the size of the chamber needed to assay a given particle energy. Small windows of aluminum alloy about $4 \text{ mg}/\text{cm}^2$ will withstand pressure differentials of a few atmospheres.

C. Electrometers

Mechanical electrometers were quickly replaced by electrometer tubes. Long-term drift of the electrometer tube was still a problem, particularly if an attempt was made to add vacuum-tube amplifiers. The conventional or dc circuits amplified both the signal and all slow fluctuations and drift as well. If the original signal is oscillatory, it can be amplified by ac circuits, which do not respond to the slower variations.

The basic scheme for selective amplification was developed in 1938 for use with thermocouples, but nine years elapsed before it was applied to ion current measurements in the dynamic-condenser electrometer (Palevsky, Swank, and Grenchik 1947). The most popular design utilized a vibrating reed (whence the popular name) to produce a cyclically varying signal from the ion chamber, and this signal was then amplified by ac circuits. Ion currents on the order of 10^{-15} A could be measured with commercially available vibrating-reed electrometers. They enjoyed a short period of popularity until replaced with new instruments.

D. Proportional Counters

Electronic circuit components and designs continued to develop after the impetus of the MED declassification. The very stable power supplies needed for proportional counting were improved. Linear amplifiers with superior resistance to overloads were designed. Tanks of counting gas-quenching gas mixtures became commercially available, and most proportional counting was done with a slow gas flow following a rapid chamber flush after inserting the sample. Commercial competition was keen to provide the most reliable and easy to use equipment. Many improvements were unpublished because they were made by profit-oriented organizations.

Developments in the MED had added high- and low-energy discriminators to the basic linear amplifier. With these discriminators in use, only pulses falling within a narrow energy "window" were counted. Background counts were sharply reduced because these also were counted through the narrow window, and there was a corresponding increase in the overall sensitivity of the system. Beta-particle-energy spectra could now be obtained, an important advance in the identification and assay of radioisotopes.

When determining energy spectra, considerable counting time can be saved by the simultaneous counting of a number of energy channels instead of by the step-by-step movement of a single channel. A twenty-channel pulse height analyzer (PHA) was reported (Freundlich, Hincks, and Ozeroff 1947), the forerunner of later equipment made possible by borrowing computer technology.

E. G-M Counters

Steady, but unspectacular improvements in G-M tube and circuit performance continued as the demands for counting equipment increased. Scale-of-ten or decade circuits were developed (Regener 1946), which could be cascaded to provide scaled readings in the decimal system. Interpolation counts still had to be added, but the old $\times 64$ calculation of the binary scalers was eliminated. Still later, decade glow transfer tubes were produced, and the exact count could be read from glowing numbers without interpolation.

For many applications, halogen quenching gases (Liebson and Friedman 1948) replaced the organic quenchers. The halogens recombine after dissociation in the quenching process and thus provide a tube with an unlimited counting life.

G-M tubes were made in many configurations in order to maximize the geometrical efficiency of the assay. End-window counters and dipping counters were among the shapes available. The interest in ^{14}C assays, where only a 0.156-MeV beta particle is emitted, stimulated the production of thin entrance windows. These windows had to withstand substantial pressure differentials because the G-M tube has an internal pressure of only perhaps one-eighth of an atmosphere. Mica became a favorite window material. Sheets could be split to 1 mg/cm² or even a bit thinner. Mica-to-metal or glass seals were developed. Carbon-14 could now be counted with a fair, if not ideal efficiency.

F. Crystal Scintillators—Old and New

In 1903, Sir William Crookes, and independently, Elster and Geitel, discovered that crystals of zinc sulfide emitted tiny flashes of visible light (scintillations) when they were struck with alpha particles. This observation was quickly utilized by Rutherford, who used an arrangement known as a spinthariscopes in his classic studies of atomic structure.

Counting the tiny light flashes seen in a microscope is a tedious job, and crystal scintillators took on a much larger role following the development of the photomultiplier or PM tube (Larson and Salinger 1940). In the PM tube, a photo-sensitive cathode "sees" the scintillations in a crystal, and the resulting photoelectrons pass on to a series of electrodes each designed to emit several electrons for each one incident upon it. Stable current gains of 10^7 or so are readily obtained, with a strict proportionality between the number of electrons collected at the output and the number originally emitted by the cathode.

Hofstadter (1948) observed scintillations produced by the absorption of gamma photons in crystals of the alkali halides. In the case of alpha and beta particles, the magnitude of each scintillation is proportional to the energy deposited in the crystal, or the energy of the particle. Photons are absorbed by more complex mechanisms, but some fraction of the scintillations will correspond to the full energy of the photon, the fraction increasing with the size of the crystal. Thus, for all three radiations, the crystal scintillator can be used as an energy spectrometer.

Sodium iodide "activated" by a slight impurity of thallium, denoted by NaI(Tl) became the most popular crystal for photon counting. The Harshaw Company, among others, produced larger and larger crystals in quantity. NaI(Tl) crystals 25 cm in diameter are available "canned" with a PM tube in a thin, moisture-proof metal cladding. Organic crystals such as anthracene have been found most useful for beta-particle counting, and zinc sulfide is still preferred for alphas.

Scintillation counters quickly became very powerful analytical tools in radioactive assays. Using upper and lower energy discriminators, the emitted energy spectrum can be scanned in a succession of small increments and an energy emission distribution obtained. With these established, assays can be made with the system set to accept only one of the characteristic energies. The effect of background counts can thus be greatly reduced, since they also will be accepted only through the narrow energy window. Heath (1957) published an extensive catalog of gamma-ray spectra obtained with crystal scintillators. The exact spectrum obtained depends upon the size of the crystal, but cross-matching between two systems is usually easy.

G. Pulse Height Analyzers

Pulse shaping circuits and magnetic "memories" in which pulses could be stored were being produced for the computer industry, and these were quickly adapted to ion pulse counting. Sorting circuits routed pulses according to size to the various compartments of the memory. After an appropriate accumulation time, they can be retrieved to provide an energy spectrum of the incident radiation.

Technical progress steadily increased the number of memory channels in the binary sequence 128, 256, 512 . . . with corresponding increases in the resolving-power of the PHAs. At the same time, faster circuits permitted more effective utilization of the very short pulse lengths characteristic of a crystal scintillation counter. Heath (1966) updated his early compilation of gamma-ray spectra with records taken with the more modern equipment.

H. Liquid Scintillators—Carbon-14 and Hydrogen-3

When ^{14}C became readily available from Oak Ridge, its importance was quickly recognized, particularly in the fields of biology and medicine. The assay techniques then available for the 156-keV betas were far from satisfactory, and a large-scale attack on the problem was mounted. Ion chambers and G-M tubes provided only a partial answer.

Sample preparation was very important in order to minimize and standardize particle absorption in the sample itself. The carbon was sometimes converted to highly insoluble barium carbonate and counts made on the dried precipitate. A series of thin weighed samples could be counted and the specific activity (counts/mg) extrapolated to zero thickness to obtain the true value with no self-absorption. Alternatively, "infinitely thick" samples were counted under constant self-absorption conditions.

Some assay methods burned the sample, converting the carbon to CO_2 . This could be frozen out in a cold trap, the remaining gases pumped off, and the CO_2 warmed and transferred to a counting chamber.^(a) Carbon dioxide is not satisfactory for G-M tube operation, although some success was achieved by blending it with CS_2 .

The introduction of liquid scintillation counting (Raben and Bloembergen 1951) was literally a technical breakthrough. In principle, a scintillating molecule

(a) [See Figure PI-1.]

such as 2, 5-diphenyloxazole, quickly shortened to PPO, is dissolved in an organic solvent such as toluene, and the sample is added. Ions produced in the solvent molecules with no loss of energy due to window or self-absorption excite the PPO, and its scintillations are observed with one or more PM tubes.

In practice, preparation of the scintillating solution is more complicated. A "wave shifter" is added to match the color of the scintillations to the spectral response of the PM tubes. A secondary solvent is frequently needed to dissolve samples that are not soluble in the primary solvent.

Technical difficulties were quickly overcome, and liquid scintillation counting became the method of choice for soft beta emitters such as ^3H (tritium), ^{14}C , and ^{35}S . The method was also used for alpha-particle assays (Basson and Steyn 1954). Birks (1964) reviewed the early work.

Liquid scintillation counting has been refined into a very powerful analytical tool. The 18.6-keV beta particle of ^3H is readily counted at a specific activity of 1 pCi/g, ^{14}C at 0.15 pCi/g. Built-in data processing capabilities permit the simultaneous assay of two components such as ^3H and ^{14}C . Highly automated equipment has been developed for the unattended assays of large numbers of samples. Bransom (1970) and Harroden and Peng (1971) have provided reviews.

I. Semiconductor Detectors

Research on the properties of semiconductors, notably silicon and germanium, increased dramatically following the discovery of the transistor, and McKay (1951) reported on their use as alpha-particle detectors. Semiconductors have a high counting efficiency, producing one ion pair for about 3 eV of energy, which is only one-tenth the energy required in other detectors. That fact, together with their remarkable energy resolving capability, stimulated the application as radiation detectors, particularly in the field of gamma-ray spectrometry.

Extreme material purity is required for the satisfactory performance of a semiconductor, and early production processes were unable to achieve the ideal. Instead, controlled amounts of an acceptable impurity were deliberately introduced. Lithium ions were diffused through a germanium crystal to produce a lithium-drifted or Ge(Li) detector. Early Ge(Li) detectors were small, but, with improved techniques, sensitive volumes of 50 cm³ became commercially available. Ge(Li) detectors had to be maintained at liquid nitrogen temperatures at all times. Eventually, sufficiently pure semiconducting crystals were produced, and lithium drifting and cryogenic temperatures were no longer required.

Detector sizes are still relatively small, and the semiconductors find their greatest application in identification by spectrometry rather than in routine assays. Energy resolutions of 1 keV or so can be obtained, and these have been used to upgrade the gamma-ray energy catalogs (Heath 1974) previously provided by solid crystal scintillators.

J. Photographic Emulsions

Medical and industrial radiography are among the greatest consumers of photographic materials, and film badges form an important part of any personnel monitoring program. However, photographic methods now play a relatively minor role in most laboratories working with radioactive materials.

Nuclear track emulsions provide a unique method for precisely locating an alpha-particle emitter at the center of the outwardly radiating tracks. A similar technique has been used with soft beta emitters such as ^3H in tissue slices, but scattering limits its application to higher-energy betas. Very small amounts of activity can be located with emulsions because of the integrating effect of long exposure times and the amplification inherent in the production of a developable silver halide grain from a single ionizing event.

The technique is invaluable when needed, but it is time consuming and requires considerable patience and skill. This is particularly true in identifying and analyzing the tracks seen in the microscope. An early description of the method (Yagoda 1949) is still useful today.

K. Human Whole-Body Counters

Technical advances on many fronts led to the construction of counters capable of directly assaying gamma emitters contained in the human body. Larger and larger solid crystal scintillators were produced, and these could be looked at by either a large PM tube or an assembly of small tubes electrically aligned to produce summed pulses.

These large crystal volumes were quickly adapted to the measurement of gamma emitters present in the human body. A group at Argonne National Laboratory (Marinelli et al. 1961) developed a technique in which a single large NaI(Tl) crystal detected gamma rays with a reasonably constant geometry from all parts of the body. The crystal had a much greater volume, and hence sensitivity, than the G-M counters available to Evans (1937). In addition, the PHA equipment used with the crystal provided gamma-ray spectra for the positive identification of the emitters.

Large PM tubes were also used in the liquid scintillator whole-body counters developed as by-products of the search for the neutrino (Anderson et al. 1961). Here the human subject was surrounded by a cylindrical annular tank containing the scintillating solution, which was viewed by a battery of PM tubes. These tubes were connected to simple pulse-height discriminator circuits because the liquid lacked the energy resolution needed to operate a PHA. The liquid counter recorded from all parts of the body with about equal efficiency and had a high sensitivity because of the large volume of the detector.^(a)

Either type of whole-body counter had a high count-rate due to natural background, and heavy shields, usually of iron, were used to reduce it. Extreme precautions had to be taken to prevent contamination of the counting rooms.

These counters opened up new areas in the study of internal emitters. In a few minutes, a gamma activity of 1 nCi or so can be measured to an accuracy of a few percent. The amount of ^{40}K naturally present can be followed in health and in disease. In a few cases, notably ^{32}P , beta emitters can be assayed through the production of bremsstrahlung, but this method is not generally applicable.

Alpha emitters can be detected only if they are accompanied by gamma radiation. A case in point is the detection of ^{239}Pu through the 20-keV x rays emitted in a small fraction of the decays. Although these photons are strongly absorbed

(a) [The human whole-body counting device using this method was developed at Los Alamos.]

in the body, they are more penetrating than the more abundant alphas. Thin, large-diameter crystals of NaI(Tl) used inside a shielded room can measure ^{239}Pu down to perhaps 10 nCi (Voeiz et al. 1976) in a reasonable counting time. When the x rays originate at depth, as in the lung, calibration of the system is uncertain because of the strong attenuation of the soft photons.

The shielding required to attain the necessary background makes the whole-body counter a massive, expensive instrument suitable for installation in only a few large active laboratories. An ingenious adaptation is the shadow-shield counter, which can be transported, though with some difficulty, and operated in areas where onsite measurements are needed. In this counter, the NaI(Tl) crystal sees only a portion of the body at any one time, and this portion lies inside a massive shield. As the patient is moved (Parker and Anderson 1967) under the shield, the crystal scans the entire body under shielded conditions.^(a)

L. Absolute Counting

For many assays, such as most tracer studies, only relative counts are needed, to be expressed as percentages of some standard internal to the particular study. Such relative counting is comparatively simple requiring only standard sample preparation and a constant counting efficiency, or geometry.

Absolute counting is required in assays designed to establish body burdens and, thus, estimate the hazards associated with internal emitters. In many cases, a constant geometry can be established to count the samples against a standard certified by some laboratory, such as the NBS.

When the counting geometry is accurately known, as in the 2π or 4π proportional counter, the disintegration rate of the sample may be readily calculated from the observed count rate. Similarly, semiconductors may have an essentially 2π geometry for alpha particles if the sources are in the form of very thin films, perhaps formed by electrodeposition from solution.

Coincidence counting provides a powerful method for the absolute counting of radionuclides that emit more than one radiation per decay and whose decay scheme is accurately known. A beta decay followed by a gamma ray will serve as an example, although gamma-gamma or alpha-gamma coincidences may also be used. One detector that has a relatively high efficiency for beta particles and another responding only to gamma rays are required for the beta-gamma measurements. The circuits are arranged so that individual count rates of the beta and gamma detectors can be obtained. An electronic coincidence circuit is then introduced, which will record a pulse only when there are simultaneous ionizations (within about 100 nsec) in the two counters. Except for some few random coincidences, which can be allowed for, each gamma count will originate from the same decay process that triggered the beta detector. From these three measurements, with appropriate corrections for background, the absolute disintegration rate of the source can be calculated, without any prior knowledge of the efficiencies of the two detectors. Coincidence counting is a very powerful technique when it can be applied.

(a) [In chapter 12, we saw application of this type of device, in crude form, to measurements of the Marshallese.]

M. Low-Level Counting

Widespread demands have stimulated the quest for instruments and techniques capable of measuring ever smaller activities, or conversely of making measurements to the desired accuracy in shorter times. Equipment is at hand for counting individual ionizing particles and for measuring the energy transferred to the detector. Little progress can be made in this direction beyond arranging the counting geometry so that the detector will intercept as many of the emissions as possible, with a limit of a solid angle of 4π .

However, all counts are made in the presence of a background count arising from extraterrestrial cosmic rays, general terrestrial radioactivity, and from contaminants in the counting equipment itself. Any reduction in this background count relative to that from the sample will result in an improved precision in the net count, or in the counting time. If the background were strictly zero, a few pulses from a sample would be significant. Lacking the ideal, strenuous efforts have been made to reduce the background count in all types of assay systems.

In some geological formations, underground laboratories are useful. Counters may be located inside massive shields, provided that the shielding reduces more than it contributes. Steel produced before the advent of radioactive fallout is particularly useful because it is free of bulk contaminants. A thorough surface cleaning will remove all manmade emitters.

A battery of counters may be located around the one counting the sample and connected in anticoincidence with it. A pulse occurring simultaneously in a shielding counter and the sample counter will be rejected since it presumably was produced by a penetrating radiation arising outside the sample (NCRP 1978).

If the nuclide being assayed has a characteristic monoenergetic emission, as an alpha particle or a gamma ray, it may be counted with a narrow energy window, which will substantially improve the sample-background count ratio. Electronic circuits are now available (Oeschger and Wahlen 1975) that analyze the rising phase of each pulse and reject those not originating in the sample under study. As in the days of the Rutherford spinthariscopes, a few detectable ionizing events have become significant, but the amount of activity needed to produce them has been decreased by a factor of perhaps 10^{10} .

N. New Phenomena

Although advances in detection sensitivity, reliability, and assay speeds have been enormous, most of the measurements made today are based on radiation effects known for well over half a century. Ionization in gases, crystal scintillation, and photographic film darkening remain the workhorses of the field. Two recent additions to the methodology are worthy of mention.

1. Thermoluminescence

When certain crystals absorb ionizing radiation, some electrons will be raised into metastable energy levels where they will remain for hours or days. This trapping in excited states is in contrast to the very prompt return to the ground state of the electrons involved in the usual crystal scintillators. The metastable states can be relieved by heating the crystal, at which time all of the trapped electrons will return to the ground state. As in the case of prompt spontaneous fluorescence, photons of visible and ultraviolet light will be emitted. Thus, the process is known as thermoluminescence and the instrument as a TLD.

When the heating and the photoelectric recording of the emitted light pulse are carried out under carefully programmed laboratory conditions, the measured response can be related to the total amount of radiation absorbed by the crystal during the exposure period. After the light pulse has been recorded, the crystal can be put through a thermal cycle of "annealing" to ensure that all electrons are back in the ground state, ready to receive a second dose of radiation.

Some crystals, notably LiF and CaF₂, each with controlled traces of impurities, have radiation absorption characteristics very close to those of human tissue. This, together with the reusability, have made TLDs increasingly important in personnel dosimetry. Attix (1972) has provided a useful review of the field.

2. Particle Track Etching

Neutrons, alpha particles, and heavier charged particles such as fission fragments, produce some structural damage when moving through solid materials.

The damage centers are very small, but they can be enlarged by chemical etching with NaOH or EDTA (ethylene diamine tetra acetic acid) to produce tracks visible in the microscope (Fleischer, Price, and Walker 1965). The number of tracks per unit area can be related to the total number of particles incident on the material. Certain plastics, glasses, and ceramics have been found useful. The technique is specialized, but it has been applied to biological dosimetry (Becker 1969).

IV. Summary and Commentary

This chapter reviews almost a century of development of radiation-measuring instruments. Obviously, the field had had almost forty-five years of development before 1940. Nevertheless, the needs of the Manhattan Project posed formidable problems for the instrumentation groups. Because of the high security classifications and to explore several avenues simultaneously, the several laboratories, e.g., Berkeley, the Metallurgical Laboratory in Chicago, the Los Alamos and Oak Ridge groups, and the project at the University of Rochester, had specific tasks in instrumentation, as well as in their research. New and unique circuitry was developed. Instruments for radiation safety purposes developed beside the more conventional laboratory measurement devices. In some cases, the instruments from the different laboratories followed different routes to the same end. At the end of World War II, when declassification made it possible for the laboratories to share and compare their products, there was some inertia toward continuing to use the familiar methods, and even to defend their superiority. As the commercial instrument makers gradually took over design and manufacture of radiation-measuring instruments and numerous symposia were held, this tendency abated.

In the period after World War II, there was, of course, an explosive expansion of the uses of radioactive materials in all branches of the natural and biological sciences. Tracer chemistry and nuclear medicine put demands on instrumentation far beyond what they would have been had the needs been only the researches described in this book. These needs and the chances for handsome financial returns brought not only improvements but essentially new devices. Among these are the scintillation counter using special solid crystals, the liquid scintillation counter, and a large expansion of the ability to do pulse height

analysis and draw complete spectra over a range of energies. The discovery of the transistor made possible very considerable reductions in size and power requirements.

Perhaps some of the most striking developments in the counting of radioactivity in the past two decades have been from uses in nuclear medicine. These devices are not described in this chapter since it was considered wise to review them briefly as part of the story of nuclear medicine in chapter 20. Scanning, imaging, and recording have developed enormously. Now, with the aid of computer print-outs, all information except suggested diagnosis and treatment can apparently be automated. While these developments have been primarily for clinical installations, the techniques have, of course, spilled over into the research laboratories. Now a day or a week can produce more and better radioactivity analyses than could have been generated in a year with the old hand-operated instruments. Unfortunately, with this has come a gulf between the researchers and knowledge of the reliability of their results. This can be bridged only by confidence in the manufacturers and their service representatives or an inordinate investment of time and energy by the researcher.

References

- Anderson, E. C., R. I. Schuch, V. N. Kerr, and M. A. Van Dilla. 1961. Humco II: A new four pi liquid scintillation counter. In *Radiation in man*, ed. G. R. Meneely. Springfield, Ill.: Charles C. Thomas.
- Attix, F. H. 1972. A current look at the TLD in personnel monitoring. *Health Phys.* 22:287-91.
- Axelrod, D. J. and J. G. Hamilton. 1948. The radioautographic technique. In *Supplement to the U.S. Naval Med. Bull.* 48:122-41.
- Basson, J. K. and J. Steyn. 1954. Absolute alpha standardization with liquid scintillators. *Proc. Roy. Soc. Ser. A.* 67:297.
- Bearden, J. A. 1933. Radioactive contamination of ionization chamber materials. *Rev. Sci. Instrum.* 4:271-75.
- Becker, K. 1969. Alpha particle registration in plastics and its applications for radon and neutron personnel dosimetry. *Health Phys.* 16:113-23.
- Birks, J. B. 1964. *The theory and practice of scintillation counting*. Oxford: Pergamon Press.
- Bransom, E. D., ed. 1970. *The current status of scintillation counting*. New York: Grune & Stratton.
- Compton, A. H. and S. K. Allison. 1935. *X-rays in theory and experiment*, p. 6. New York: Van Nostrand.
- Curtiss, L. F., C. Goodman, A. S. Kovarik, S. C. Lind, C. S. Piggot, and R. D. Evans. 1940. Radioactive standards. *Rev. Sci. Instrum.* 11:205.
- DuBridge, L. A. and H. Brown. 1933. An improved d.c. amplifying circuit. *Rev. Sci. Instrum.* 4:532-36.
- Evans, R. D. 1937. Radium poisoning II. The quantitative determination of the radium content and radium elimination rate of living persons. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* 37:368-78.
- Evans, R. D. and R. L. Alder. 1939. Improved counting rate meter. *Rev. Sci. Instrum.* 10:332-36.
- Failla, G. 1937. The measurement of tissue dose in terms of the same unit for all ionizing radiations. *Radiology* 29:202-15.
- Fleischer, R. L., P. B. Price, and R. M. Walker. 1965. Tracks of charged particles in solids. *Science* 149:383-93.
- Freundlich, H. F., E. P. Hincks, and W. J. Ozeroff. 1947. A pulse analyzer for nuclear research. *Rev. Sci. Instrum.* 18:90-100.

- Fricke, H. and O. Glasser. 1925. Eine theoretische und experimentelle Untersuchung der kleinen Ionisationskammer. *Fortschr. Geb. Röntgenstr. Nuklearmed.* 33:239-50.
- Geiger, H. and W. Müller. 1928. Das Elektronenzählrohr I. Wirkungsweise und Herstellung eines Zählrohrs. *Phys. Zeit.* 29:839-41.
- Glasser, O., U. V. Portmann, and V. B. Seitz. 1928. The condenser dosimeter and its use in measuring radiation over a wide range of wave lengths. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* 20:505-13.
- Gray, L. H. 1936. An ionization method for the absolute measurement of γ -ray energy. *Proc. Roy. Soc. Ser. A.*, 156:578-96.
- Harroden, D. L. and C.-T. Peng, eds. 1971. *Organic scintillators and liquid scintillation counting*. New York: Academic Press.
- Heath, R. L. 1957. *Scintillation spectrometry, gamma-ray spectrum catalog*. AEC report IDO-16408. Washington, D.C.: U.S. Atomic Energy Commission.
- Heath, R. L. 1966. Computer techniques for the analysis of gamma-ray spectra obtained with NaI and lithium-ion drifted germanium detectors. *Nucl. Instrum. Methods* 43:209-29.
- Heath, R. L. 1974. *Gamma-ray spectrum catalogue, Ge(Li) and Si(Li) spectrometry*, Aerojet Nuclear Corp., ANCR-1000-2, vol. 2. Washington, D.C.: U.S. Atomic Energy Commission.
- Higinbotham, W. A., J. Gallagher, and M. Sands. 1947. The model 200 pulse counter. *Rev. Sci. Instrum.* 18:706-15.
- Hofstadter, R. 1948. Alkali halide scintillation counters. *Phys. Rev.* 74:100-101.
- Jauncey, G. E. M. 1938. Heavy beta-rays from RaE. *Phys. Rev.* 53:197.
- Jordan, W. H. and P. R. Bell. 1947. A general purpose linear amplifier. *Rev. Sci. Instrum.* 18:703-5.
- Lacassagne, A. and J. S. Lattès. 1924. Méthode auto-histo-radiographique pour la détection dans les organes du polonium injecté. *C. R. Hebd. Séances Acad. Sci.* 178:488-98.
- Larson, C. C. and H. Salinger. 1940. Photo-cell multiplier tubes. *Rev. Sci. Instrum.* 11:226-29.
- Lauritsen, C. C. and T. Lauritsen. 1937. A simple quartz fiber electrometer. *Rev. Sci. Instrum.* 8:438-39.
- Lawrence, E. O. and M. S. Livingston. 1932. The production of high speed light ions without the use of high voltages. *Phys. Rev.* 40:19-35.
- Liebson, S. H. and H. Friedman. 1948. Self-quenching halogen-filled counters. *Rev. Sci. Instrum.* 19:303-6.
- Lifschutz, H. 1939. A complete Geiger-Müller counting system. *Rev. Sci. Instrum.* 10:21-26.
- Marinelli, L. D., C. E. Miller, H. A. May, and J. E. Rose. 1961. The use of low level gamma scintillation spectrometry in the measurement of activity in human beings. In *Radioactivity in man*, ed. G. E. Meneely, p. 16. Springfield, Ill.: Charles C. Thomas.
- McKay, K. G. 1951. Electron-hole production in germanium by alpha-particles. *Phys. Rev.* 84:829-32.
- Metcalf, G. F. and B. J. Thompson. 1930. A low grid-current vacuum tube. *Phys. Rev.* 36:1489-94.
- National Bureau of Standards. 1961. *Stopping powers for use with cavity chambers*. NBS Handbook 79. Washington, D.C.
- National Council on Radiation Protection and Measurements. 1978. A handbook of radioactivity measurements and procedures, NCRP report no. 58. Washington, D.C.
- NBS. See National Bureau of Standards.
- NCRP. See National Council on Radiation Protection and Measurements.
- Neher, H. V. and W. H. Pickering. 1938. Modified high speed Geiger counter circuit. *Phys. Rev.* 53:316.
- Oeschger, H. and M. Wahlen. 1975. Low level counting techniques. *Ann. Rev. Nuc. Sci.* 25:423-63.
- Palevsky, H., R. K. Swank, and R. Grenchik. 1947. Design of dynamic condenser electrometers. *Rev. Sci. Instrum.* 18:298-314.

- Parker, D. and J. I. Anderson. 1967. A portable whole-body counter. *Health Phys.* 13:141-48.
- Raben, M. S. and N. Bloembergen. 1951. Determination of radioactivity by solution in a liquid scintillator. *Science* 114:363-64.
- Regener, V. H. 1946. Decade counting circuits. *Rev. Sci. Instrum.* 17:185-89.
- Rossi, B. B. and H. H. Staub. 1949. Ionization chambers and counters. In *National Nuclear Energy Series*, div. V, vol. 2. New York: McGraw Hill.
- Shapiro, M. M. 1941. Tracks of nuclear particles in photographic emulsions. *Rev. Mod. Phys.* 13:58-71.
- Simpson, J. A., Jr. 1947. A precision alpha-proportional counter. *Rev. Sci. Instrum.* 18:884-93.
- Strong, J. 1947. *Procedures in experimental physics*, 13th printing 1947. Englewood Cliffs, N.J.: Prentice-Hall, Inc.
- Taylor, L. S. 1929. The precise measurement of x-ray dosage. *J. of Res.* 2:771-85; and Analysis of diaphragm system for the x-ray standard ionization chamber. *J. of Res.* 3:807-27. Washington, D.C.: National Bureau of Standards.
- Taylor, L. S. 1958. History of the International Commission on Radiological Units and Measurements (ICRU). *Health Phys.* 1:306-14.
- Trost, A. 1937. Über Zählrohre mit Dämpfzusatz. *Zeit. für Physik* 105:399-444.
- Van de Graaff, R. J., K. T. Compton, and L. C. Van Atta. 1933. The electrostatic production of high voltage for nuclear investigations. *Phys. Rev.* 43:149-57.
- Voelz, G., J. Umbarger, J. McInroy, and J. Healy. 1976. Considerations in the assessment of plutonium deposition in man. In *Diagnosis and treatment of incorporated radionuclides*, STI/PUB/411, pp. 163-76. Proceedings of an international seminar held in Vienna, December 8-12, 1975. Vienna: International Atomic Energy Agency.
- Yaffe, L. 1962. Preparation of thin films, sources, and targets. *Ann. Rev. Nuc. Sci.* 12:153-88.
- Yogoda, H. 1949. *Radioactive measurements with nuclear emulsions*. New York: John Wiley & Sons.

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Capsule Chronology

Prior to 1930 A few field measurements made by cosmic-ray physicists. The spinthariscopes developed. Many instruments built for portable use in medical installations, e.g., Victoreen R-Meter, film badges.

1929 Taylor portable survey meter.

1930s Some field-type instruments developed as modifications of laboratory instruments, e.g., Geiger-Müller counters, film badges. In general, better for external sources than measurement of radionuclides.

Evans adapts count-rate circuitry to a mobile machine, develops a double ionization chamber for radon, and an ac-operated device for thoron (Evans and Goodman).

Expired air analyses for radon and thoron made using gold-leaf electroscope.

1940s MED^(a) uses electrostatic precipitator and suitable detector for measuring airborne activity. Also static evacuated sampling flasks for grab samples that are subsequently analyzed in the laboratory.

MED adapts use of filter papers, as used in industrial hygiene, to measurements of radioactivity. Leads to development of continuous air-monitoring devices with collection and measurement assembled in one unit.

MED develops many devices with code names because of security restrictions. Examples:^(b)

"Pee Wee," a heavy, bulky air-proportional counter used at Los Alamos and Berkeley for alpha surface contamination monitoring.

"Juno," a large ionization chamber with a thin window for alpha or beta-photon monitoring of bench tops, etc. (Note: the "Juno" with appropriately modernized circuitry is still being manufactured.)

"Poppy," an alpha counter using a photomultiplier tube and scintillation counter. Audible clicks can be replaced by count meter.

"Samson," like Juno, but intended for alpha-particle measurements only.

"Cart poppy," an ac-operated, more stable, more bulky version of the Poppy.

"Pluto," an instrument developed especially for monitoring of plutonium and related alpha-emitting radionuclides. The allusion to the highly classified radionuclide, plutonium, produces an outburst from General Groves.

"Sniffy," an air monitoring device.

Cascade impactor developed in U.K.—adapted to U.S. operations in late 1940s.

(a) [For abbreviations and acronyms, see Appendix D.]

(b) Many other picturesque names were applied to other instruments used for radiation exposure or dose determination, rather than for radionuclide detection and measurement, e.g., "Cutie Pie," "Chang and Eng," "Paint Pail," "Zuto," etc.

Marked improvements made throughout the period, including thin-window counters, Schmidt trigger circuit, thyratrons, flip-flops, uni- and multivibrators, binary and later decade scalers. Use of small high-resistance, low-current drain tubes, developed originally for hearing aids and lower voltage G-M tubes. (See also chapter 17.)

1950s Air sampling and monitoring devices change little except for addition of spectrometry.

Two-stage sampling devices introduced instead of cascade impactor as less complex and easier to use.

Moving filter air monitor developed.

Continuous gas monitors developed for low levels of beta emitters. Called "Sniffers."

Midget cyclone developed.

Development of scintillation techniques makes continuous monitoring of radon concentrations easier.

Beginning of working level measuring systems for radon and daughters (Kusnetz).

Search for thinner and thinner windows for alpha instruments.

Search for new quenching gases.

1957 Lucas cell developed for measurement of grab samples to be analyzed for radon and progeny.

Portable gas flow proportional counter developed for alphas (Eberline).

1960s Air monitoring for plutonium developed using semi-conductor detectors, now the mainstay for monitoring plutonium in work-room air.

1963 Portable whole-body counters taken to Marshall Islands (Cohn, Brookhaven).

Truck-mounted shadow shield whole-body counters developed at Hanford and later go into general use, including in the Arctic.

Mid-1960s Radon film badge.

1969 Development of FIDLER, a scintillation detector for large area surveys of outdoor surfaces.

1970 Two-filter method for radon and radon daughters.

Integrating working level meters appear.

1971 Track-etch techniques for alpha particle monitoring.

1973 ANSI adapts Kusnetz method for monitoring uranium mines.

"Instant" working level meter developed (Groer, Evans, Gordon).

1977 Other working level measurement systems developed (Schiager, Shreve, et al.).

1980s Miniaturization, almost exclusive use of solid-state circuitry, reliability improvements.

Chapter 18

Instrumentation for Monitoring and Field Use^(a)

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Overview

In this chapter, the evolution of field instrumentation for the detection and quantification of internal emitters is traced. The history of field instrumentation largely begins (and to some extent ends) with the Manhattan District, for, prior to that time, there was little impetus for field measurements of internal emitters. Those halcyon few years of the Manhattan District were marked by an intensity of development and discovery that clearly set the stage for what was to follow, as even the casual reader should not fail to note. Perhaps the excitement and zing faded in later years, but the basic concepts for field instrumentation first put forth in the forties remain.

This brief chapter shows how the knowledge of the hazards of internal emitters gained in the laboratory was applied to field measurements to ensure the safety of those working in the laboratories and production facilities, and thus provides an interesting counterpoint to the main theme of our book.

(a) As used in the context of this chapter, field measurements are those that are made outside of the laboratory, normally in the workplace or the environment and generally for radiation protection purposes. Thus, field instrumentation implies a degree of ruggedness to permit transportability to and use in situations in which various environmental conditions (e.g., temperature, humidity, supply voltage) are uncontrolled. Monitoring instrumentation is instrumentation used for measurement (as opposed to sampling) under diverse conditions, in the plant, laboratory, or in the field.

The term "direct counting" refers to counting of the sample with no pretreatment or radiochemistry of any kind. Direct counting thus applies to situations in which the sample, as it is collected, is counted in situ in a monitoring device or where a sample is collected and simply brought into the laboratory for counting. Samples that undergo dissolution, chemical separation, or dilution would thus not be considered to be directly counted.

I. Before the Manhattan Engineer District

In the historical record, the Manhattan Engineer District (MED) marks the real point of origin for field measurements of radioactivity, particularly in living organisms, although there was some effort in this regard before 1940. Prior to about 1930, radiological measurements were largely confined to the laboratory, although exceptions did exist. Physicists studying cosmic rays travelled to various parts of the world, their major field instrumentation consisting of thick photographic emulsions or large, bulky electrometers and Geiger-Müller (G-M) tubes with associated electronics. Some field measurements had also been made of naturally occurring terrestrial radiations and radioactivity, using basically the same techniques and instruments. Common practice, however, was to obtain a sample of the environmental medium of interest by whatever convenient means and transport it to the laboratory for analysis. What instrumentation was available was largely used in the laboratory and, if taken into the field, as was sometimes done, was used in a manner that was largely an extension of laboratory techniques and not in the sense of an instrument capable of independent operation under field conditions.

Genuine interest in field measurement of radionuclides began as the hazards of internal radium began to be recognized. This interest was primarily in measurements of radioactivity in the environment. By contrast, laboratory measurements also included detection and quantification of radioactivity within the body. As the tragic story of the dial painters unfolded, the need for instruments to determine radiological conditions directly in the field was recognized, but, on the eve of the entry of the United States into World War II, there was precious little field instrumentation applicable to the detection and measurement of radioisotopes either in or out of the body. The few field measurements that were made were usually accomplished with laboratory instruments brought into the field for ad hoc use and hence were simply extensions of laboratory operations. There was but a single commercially available survey meter—a Geiger-Müller instrument constructed by Victoreen Instruments—and this device was not particularly suited to contamination monitoring (Kathren 1980; Terry 1980). This lack of field instrumentation is not too surprising, for there was no real basis or need for quantitative field measurements, given the lack of standards for permissible concentrations of radioactivity in air and water or as surface contamination. The first such standard—10 pCi/l for airborne radon—was proposed in 1940 and incorporated into *National Bureau of Standards Handbook 27*, issued May 2, 1941, which later became Report No. 5 of the National Committee on Radiological Protection (Evans 1980).

II. Early Evolution of Field Instrumentation

As alluded to above, fully a quarter of a century after the discovery of x rays and radioactivity, only a handful of instruments had been devised for measurement of radioactivity and radiation levels in the field. Perhaps the oldest of these instruments was the spinthariscopes, devised by Sir William Crookes in the early 1900s (Crookes 1903). This simple device was a small, light-tight metal tube about an inch in diameter and a few inches in length fitted with a ZnS screen at one end and an eyepiece at the other. A small quantity of an alpha-emitting material, such as a uranium-bearing mineral or compound of radium, could be placed directly on the screen, and the resulting flashes of light or scintillations

produced in the ZnS could be observed through the eyepiece in a darkened room. Quantitative measurements could be made by simply counting the number of flashes in a given time period and correlating them with the amount of material present.

Crooke's spinthariscopes were used for a half century, and for many years these simple passive devices enjoyed not only applications as a tool for scientists but also as entertainment for the general public, who purchased them in large numbers for parlor displays of the phenomenon of radioactivity. However simple and crude, it seems to have been the only true field instrument for measurement of radioactivity for many years. Early field measurements were ordinarily concerned with quantification of radiation sources such as x-ray machines (as opposed to radioactivity)^(a) and were generally applied to the radiotherapy setting. Thus, in the 1920s, the familiar condenser ionization chambers made their appearance with the most familiar American-made unit, the Victoreen R-meter, becoming available in 1927 (Victoreen 1944). Photographic films were used for routine personnel monitoring at least as early as 1921, often taking the form of a small piece of film or dental x-ray packet partially covered by a penny or paper clip (Pfahler 1922). The first true film badge was devised a few years later by New York radiological physicist Edith Quimby who used metal filters to compensate for the variable sensitivity of the photographic emulsion as a function of x-ray energy (Quimby 1926).

The first portable survey meter made its appearance in 1929. It was developed by Lauriston Taylor, then of the National Bureau of Standards (NBS), to monitor his own potentially hazardous exposure to an x-ray beam (Taylor 1967). This device was equipped with three interchangeable chambers of different sizes to allow for measurement of various intensities and was in every sense a true field instrument. It had, however, no application to internally deposited radionuclides (colloquially referred to as internal emitters), being useful only for measurement of external radiation fields.

Interest in field measurements of radionuclides, specifically radium, grew in the 1930s, fueled in large measure by the tragic deaths of wealthy Pittsburgh industrialist Eben M. Byers, a consumer of a radium-containing patent medicine, and the radium dial painters. The decade of the 1930s saw the birth of in-vivo counting and also the development of radon breath analysis along with the numerous improvements in laboratory instrumentation. Major advances in counting electronics were made including basic scaling circuitry, first built by the British physicist C. E. Wynn-Williams in 1932 (Wynn-Williams 1932), based on the so-called flip-flop circuitry or Eccles-Jordan trigger, which made its appearance in 1918 (Eccles and Jordan 1919). Geiger-Müller detectors were greatly improved, and in the mid-1930s, Robley Evans and his coworkers at Massachusetts Institute of Technology (MIT) adapted the count rate circuitry to practical use making possible field survey and counting instrumentation. Among the first applications was a portable direct reading random pulse count rate meter equipped with a G-M tube as a detector used by Evans in his studies of radium metabolism in man (Evans 1980).

The MIT counting rate meter, as it was then termed, was first described in 1936 (Gingrich, Evans, and Edgerton 1936) and was basically an electronic amplifier and computing circuit with dc current or voltage output proportional to the number of pulses fed into the circuit via a G-M tube. As the early G-M

(a) Gamma rays from radium or the radium decay chain were the notable exception.

tubes were not self-quenching,^(a) the preamplifier was used for quenching (Kip and Evans 1941; Kip et al. 1946). Pure hydrogen, which has no metastable states, was also recommended as the fill gas to avoid the quenching problem (Duffendack, Lifschutz, and Slawsky 1937). Subsequent improvements included a strip chart recorder and an internal calibration circuit based on a multivibrator pulse generator synchronized to various multiples of the 60-Hz line frequency. While obviously not a field instrument per se, the MIT counting rate meter circuitry was amenable to adaptation to battery power and to use in portable instruments and was therefore in effect a historical antecedent of numerous instruments developed for use in the field. Another important contribution of the MIT group to both laboratory and field measurement problems was an early and thorough consideration of the statistical aspects of count rate meter results (Schiff 1936; Schiff and Evans 1936). This work was in part the product of the same Robley Evans, who figured so prominently in the studies of the radium dial painters, and his colleague, Leonard I. Schiff, who became well known for his contributions to theoretical physics and quantum mechanics, and, in conjunction with the theoretical evaluation of scaling circuit statistics published the following year (Alaoglu and Smith 1938), provided an important underpinning to the application of instrumentation to measurement of low-level radioactivity in the field.

Other circuitry was developed to provide solutions to the quenching problem. C. E. Wynn-Williams patented an external quenching circuit and also constructed G-M tubes capable of satisfactory operation at only 300 V (Lewis 1943). The Wynn-Williams circuit used a thyratron to drive a recording counter. Multivibrator circuits were also used for external quenching, and a significant body of literature developed on the theory and practice of external quenching by electronic circuitry.

Perhaps the single field measurement for internal emitters that was well developed prior to World War II was the so-called breath analysis, or analysis of the exhaled air for both radon and thoron. In his pioneering studies on the metabolism and fate of ingested radium, Evans determined a relationship between the amount of radium in the body and the quantity of radon in the expired air (Evans 1937). Initially, radon was measured by collecting the expired air in an ionization chamber attached to a gold-leaf electroscope; subsequently, the method was improved to include electrostatic collection (Aub et al. 1952). More recent techniques include having the subject blow up a balloon, which is then examined for long-lived radon daughters. The original gold-leaf electroscope technique was used in the field by the University of Missouri from 1930 to 1936 for detection of thoron in the expired air of mesothorium (i.e., ^{226}Ra , ^{228}Ac) workers (Morris 1938).

III. Air Sampling and Monitoring: MED

In general, until the MED was organized in the early 1940s, field sampling and measurement of internal radioactivity hazards were largely carried out by industrial hygienists and perhaps an occasional physicist using the standard collection techniques of the time for measurement of nonradioactive dusts (Drinker and Hatch 1947) (see figures 18.1 and 18.2). These included dust collection via

(a) [See chapter 17.]

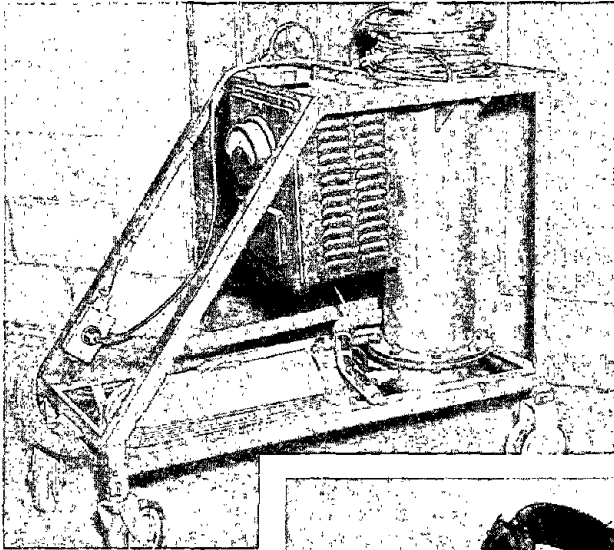
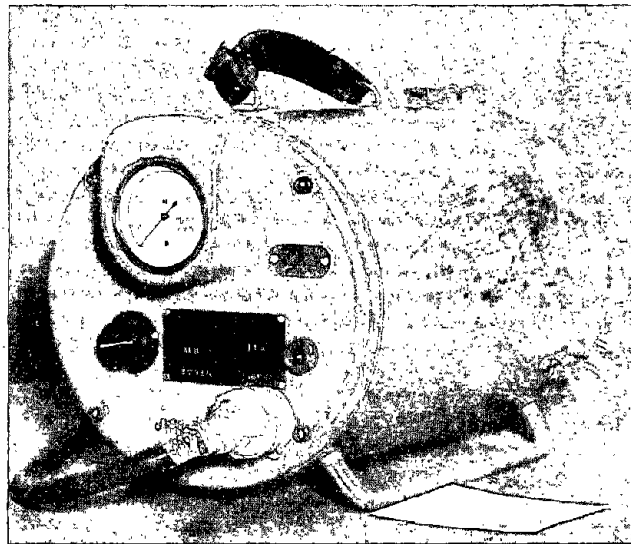


FIGURE 18.1. (Left) A portable air sampler, late 1940s. The air mover for this cart-mounted unit was an Electrolux vacuum cleaner (lower left). (Photo courtesy of Pacific Northwest Laboratory.)

FIGURE 18.2. (Right) Mine Safety Appliances Co. air sampler of the type used in the field during the 1940s and beyond. (Photo courtesy of Pacific Northwest Laboratory.)



impingers of the Greenburg-Smith and other types with subsequent particle and radioactivity counting, or the use of electrostatic precipitators to obtain a dust sample, which could then be counted for radioactivity in the laboratory. One technique specific for field sampling of thoron daughters was developed at MIT (Evans and Goodman 1940); it utilized an air mover to deposit the dust-borne daughters of thoron (i.e., ^{212}Pb and progeny) onto planchets, which were then returned to the laboratory for analysis (Evans and Goodman 1940). Thus, on the eve of the formation of the MED, field instrumentation for sampling and measurement of radioactivity in the workplace or the environment gave no hint of the heightened interest and dramatic changes that would take place over the next few years.

Electrostatic precipitators were better suited to field measurement of radioactive dusts than impingers since the material removed from the air was deposited dry on the inner surface of the cylindrical metal precipitator tube and could be directly and easily measured in the field if necessary with a G-M detector

inserted directly into the precipitator tube. Collection with Greenburg-Smith or similar impingement devices was necessarily wet, often requiring relatively lengthy laboratory analysis with concomitant delay. The standard impinger had a fairly high sampling rate—11.5 ft³/min—but the overall efficiency of the collection and counting system was low, typically only 0.5% (Nickson 1951).

Electrostatic precipitation was thus a preferred air sampling method during the early days of the MED (Morgan 1948). The typical electrostatic precipitator was a standard commercially made ac-powered unit weighing approximately thirty-one pounds. Samples collected with this device could be used for measurement of alpha as well as beta-photon emitters depending on the type of detector used for readout. Common practice was to collect the sample in the field and take the precipitator tube to the laboratory for a timed count using a binary scaler.

Also used in the early days of the MED were static evacuated sampling flasks known as vacuum cans or pigs (see figure 18.3). These appropriately named metal devices provided the means of obtaining a grab sample of a known volume of room air, which could then be counted for beta-photon activity in the laboratory with a G-M detector. Another use of the evacuated can was for the collection and analysis of samples of radioactive gases such as ⁴¹Ar. Sampling was in the field followed by laboratory analysis, which was accomplished by connecting the metal can to an electrometer (Morgan 1949).

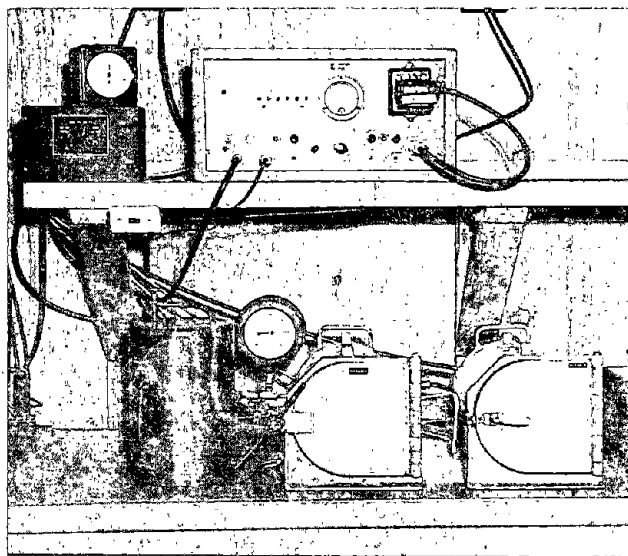


FIGURE 18.3. Counting system for gas and particulate air samples, dating from Manhattan District days. A portable gas sampling flask, commonly called a pig, is shown in the lower left. (Photo courtesy of Pacific Northwest Laboratory.)

An important contribution of the early MED to field instrumentation for internal emitters lay in the application and development of air sampling techniques involving the removal of particulate radioactivity from an air stream with filter papers, which could then be directly examined or counted in the laboratory with G-M tubes or other detectors. To be sure, the filter sampling techniques did not originate in the MED but had been used previously by industrial hygienists for nonradioactive dusts (see figures 18.3, 18.4, 18.5). Although in many respects not particularly well-suited to nonradiological applications, except perhaps for gravimetric dust measurements, the filtration method was almost perfectly suited to evaluation of airborne radioactivity. Initial techniques

were quite simple and involved a simple air mover such as a vacuum cleaner motor pulling air through a standard laboratory filter paper on which the air-borne dust was collected. Both the filter technique and electrostatic precipitation were found to be satisfactory for routine use in sampling workroom air, although the potential errors associated with samples collected outside the breathing zone were recognized (Nickson 1951). Moreover, both types of samplers were used on a spot-check as well as continuous basis, both within the plant and in the plant environs (Cantril and Parker 1945; Morgan 1948). Continuous air sampling and monitoring were also routinely accomplished on gaseous effluent lines.

FIGURE 18.4. (Right) Entering a radiation zone during Manhattan District days. The instrument in the foreground is a portable air sampler, the air mover motor is mounted on the little wheeled cart and draws air into the duct, which begins just to the left of the door knob, down through a filter housed in the box near the knee of the monitor. (Photo courtesy of Pacific Northwest Laboratory.)

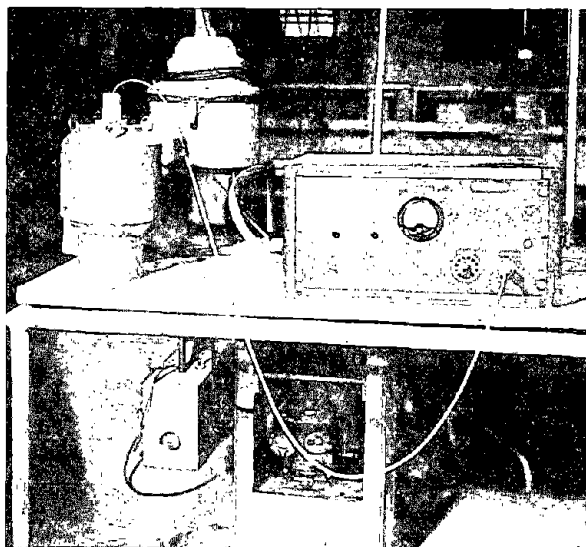


FIGURE 18.5. (Left) An air monitoring system dating back to the Manhattan District. (Photo courtesy of R. L. Kathren.)

The basic continuous air monitor used in the MED evolved about 1944 and consisted of several individual components connected together to provide an integral unit (see figures 18.3 and 18.5). Air was drawn continuously through a paper filter by a vacuum cleaner motor. The filter was rolled into a cylinder around a G-M tube and was directly counted for beta-gamma radiation as the dust was collected. To increase sensitivity and minimize interference from background radiation, the filter and G-M detector assembly were housed in a lead-shielded enclosure. The signal from the detector was generally fed into a count rate meter, which in turn drove a standard commercial recorder (Morgan 1948, 1949). Modern air monitoring equipment is essentially identical conceptually, although more sophisticated detectors, electronics, and alarm systems are in use.

Collection of alpha activity in air was generally accomplished by electrostatic precipitation. The alpha-bearing airborne dust was deposited on a thin aluminum sheet lining the inside of the collecting cylinder. This sheet was removed carefully after the sampling period and taken to the laboratory where it was counted by alpha proportional counters (Morgan 1950).

Despite its many technical advantages, air sampling by electrostatic precipitation never was a highly popular technique. The necessity for cleaning the collector was a minor inconvenience. More troublesome were the need for ac power as well as the relatively large bulk and weight of the instrument—more than 20 kg in some instances—and the inconvenient and disconcerting arcing that occurred during the collection procedure, particularly in humid atmospheres.

IV. Electronics and Counting Instrumentation

To a great extent, evaluation of radionuclides in the field was facilitated by the advances in electronics and counting instrumentation that devolved from the MED and that have been detailed in two of the volumes of the National Nuclear Energy Series (Rossi and Staub 1949; Elmore and Sands 1949), chapter 17 herein, as well as in numerous internal and open literature reports. These experimental efforts led to the development of reliable and reproducible counters such as a thin-walled G-M tube designed at the Metallurgical Laboratory for use as a beta counter and the thin mica end-window G-M tube. Both of these, but in particular the latter, were extremely useful for counting samples of radioactive dust removed from the air and were quickly applied to this purpose. In general, alpha counting of air samples in situ was not accomplished with early field instrumentation, although appropriate detectors were potentially available.

Another significant advance was the development of practical scintillation detectors (see chapter 17). Initially, the scintillation phenomenon had been used by Rutherford and other pioneers who observed and counted individual scintillations with the aid of a microscope, a difficult, tedious, and error-prone procedure. By 1930, scintillation counting was replaced by G-M counting, which offered greater flexibility, accuracy, range, and other advantages. But about 1940, interest in scintillation counting was rekindled by the development of the photon-tube counter, a hybrid detector that joined a scintillator to a photo-sensitive G-M tube (Krebs 1955). Further work with scintillators in the latter days of the MED led to the development of the modern scintillator-photomultiplier combination (Curran and Baker 1944), which has been widely utilized for

detection and measurement of radionuclides of concern in the field. For alpha-emitting radionuclides, ZnS, operable at room temperatures, quickly became the detector of choice (Ahearn 1948, 1949) and to this day is still widely used for detection of alpha contamination from plutonium and other important radioisotopes in the field.

For beta and photon counting, the G-M tube remained the primary detector. Solution of the quenching problem (chapter 17) led to the ability to use G-M detectors at higher counting rates, ranging to 10^6 counts per minute. Organic quenched tubes were widely used throughout the 1940s but showed a finite lifetime just as did the laboratory instruments because of dissociation of the organic component of the fill gas. This problem was overcome to a great extent by use of halogen-quenched tubes, which made their appearance during the 1950s.

The electronics advances in other areas were in many instances truly striking. Among these were the Schmidt trigger circuit, a type of voltage discriminator that made possible fast counting and was widely used as the basis for several of the "standard" counters that were developed during the war. These included the Model 220 and Model 600 counters. The Model 220 counter was designed to use only miniature tubes and thus was especially suited to portable applications. The Model 600 counter was designed for higher counting rates, and featured a scale of eight (i.e., three consecutive Schmidt triggers) based on the design by Shepherd and Haxby (1936), with a resolving time of only $0.7 \mu\text{sec}$ (Sands and Elmore 1949). Other triggering circuitry was also developed and used including thyratrons, and various flip-flops, univibrators, and multivibrators.

Triggers were, of course, applied to scale-of-two circuits, giving rise to widespread use of the binary scaler. Also developed during the war years was a satisfactory scale-of-ten or decade scaler, which provided the count data in the far more convenient decimal readout. This circuit consisted essentially of a scale-of-sixteen circuit plus an additional flip-flop, which was designed to cut off the upper six counts, permitting operation as a scale-of-ten device. The output from either the first or subsequent decade was used to drive an electro-mechanical register, which produced a direct decimal readout of the number of counts, thereby obviating the need for conversion from the binary readout and reducing errors (Elmore 1949; Sands and Elmore 1949) (see figure 18.6). A commercial decade scaler based on this circuitry was available at least as early as 1947, offered by the Potter Instrument Company of Flushing, New York. This device was designed to operate with G-M tubes and featured three plug-in type decades and a resolution time of $5 \mu\text{sec}$ (Nucleonics staff 1948).

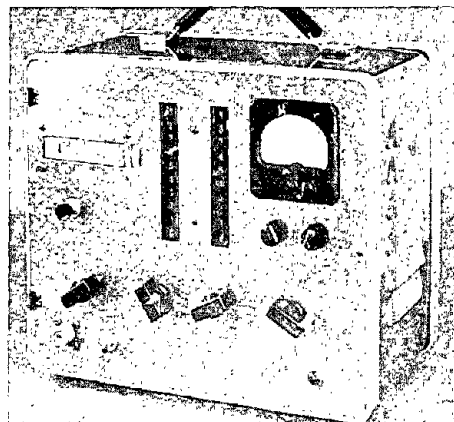


FIGURE 18.6. An early decade scaler, of commercial manufacture, circa 1950. Although equipped with a handle, this ac-powered unit was not specifically designed for field use. (Photo courtesy of R. L. Kathren.)

Other electronics developments of significance to field measurements of radioisotopes during the war included improvements in linear voltage amplifiers, which, when taken together with the improved detectors, provided a greatly enhanced field monitoring capability. One such amplifier was a relatively simple ac-operated dc amplifier, which was found to be quite useful in the workplace for continuous monitoring purposes using an ionization chamber detector. This amplifier used only two vacuum tubes, both pentodes, and provided an output signal suitable for driving a standard commercial 1 mA recorder (Elmore 1949).

The discovery of the transistor and the development of solid-state electronics were important quantum jumps for field monitoring. The solid-state revolution not only made possible smaller lightweight instruments with improved reliability and freedom from environmental factors, but also eliminated dependence on ac power or heavy battery packs. Thus, an entire new family of hand-held contamination-monitoring instruments began to evolve during the 1950s. By mid-decade, these were featured in commercial lines of instrumentation, and the venerable workhorses, such as the cart poppy (figure 18.7) and Pee Wee, began to be replaced by smaller and more reliable units. Alternating-current-powered transistorized rate meters used as laboratory bench monitors or as station monitors for monitoring personnel exiting radiation zones also appeared in the middle 1950s, with the Hanford designed "Scintran" in the vanguard. The name "Scintran" was derived from the words scintillation and transistor; the

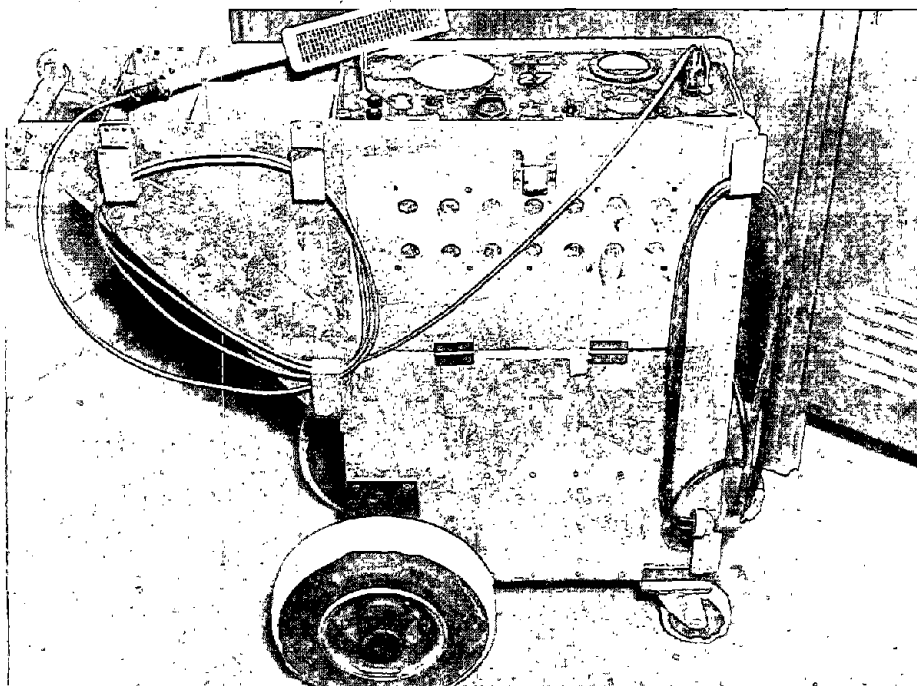


FIGURE 18.7. An early (circa 1945) cart-mounted ac-powered alpha survey meter for field use. Ac power was required to achieve the requisite stability for the air proportional probe shown atop the unit. (Photo courtesy of Pacific Northwest Laboratory.)

Scintran was a transistorized rate meter equipped with audible variable set alarm and ZnS scintillation detector that was designed for use as a personnel alpha-contamination monitor. Solid-state electronics, coupled with solid-state detectors, also led to development of an alpha air monitor suitable for detection of maximum permissible concentration (MPC) levels of plutonium about 1960 (Lindeken and Phillips 1961).

V. Later Developments in Air Monitoring

Within a few years after the close of World War II, field sampling and monitoring for airborne particulate radioactivity were fairly standardized and more or less routine operations. Typical methods were described in the open literature, with particles in air most conveniently and commonly sampled by means of various types of filters, usually glass fiber or cellulose acetate. Common practice for grab samples was to use a high-volume air sampler, which drew air through a filter with an area of 10 to 20 in.² at a rate of 30 to 70 ft³/min (figure 18.8). These samplers used commercially available vacuum cleaner motors (Schulte and Hyatt 1954). There has been substantially little change in this technique over the years.



FIGURE 18.8. A portable high volume air sampler in use at the Hanford Laboratories about 1955. Substantially the same instruments are in use today. (Photo courtesy of Pacific Northwest Laboratory.)

For continuous air sampling, a commonly used technique was based on the adaption of a standard commercial vacuum cleaner (the Filter Queen) to draw a sample of air through a 4 x 9 in. filter paper at a flow rate of 4 ft³/min. Constant air flow was maintained with a variable orifice regulator (Schulte and Hyatt 1954). Numerous other samplers were also used, but almost all were based on air filtration; electrostatic precipitation, impaction, and impingement techniques were only occasionally used, if at all.

Indeed, by 1950, the basic design for continuous air samplers and monitors for particulate radioactivity in air that would be used for the next three decades was, for all practical purposes, fully developed. Granted that monitors would become smaller with the advent of transistors and solid-state circuitry and that some sophistication would be achieved through the use of spectrometry. But all in all, the basic methods would not be appreciably changed; in more than one instance, the commercial particulate radioactivity monitor of 1950 would be very

similar in both physical appearance, design, and capability to its modern descendant of the 1980s, perhaps even to the extent of utilizing identical components such as air movers and detectors.

An exception to the above generalization was the development of a constant monitor for plutonium in air, which occurred in the early 1960s. This was made possible by the development of high-resolution solid-state semiconductor detectors which, when used in conjunction with a single-channel analyzer, allowed for relatively good differentiation of the 5.15- and 5.13-MeV alpha particles associated with plutonium decay from alpha particles of other energies associated with the decay of radon daughters. Early devices of this type were subject to significant interference from radon daughters, but still were able to detect one MPC of plutonium in air in a typical eight-hour work shift (Phillips and Lindeken 1963). Subsequent improvements in both resolution and sensitivity of the detectors and associated electronics made possible sophisticated background suppression techniques, which enhanced sensitivity by about a factor of two, but greatly increased reliability and reduced false alarms.^(a)

The solid-state alpha spectrometry monitoring device for plutonium in air has remained essentially the same for about two decades, although in recent years considerable attention has been given to other techniques. A mass spectrometry technique has been developed (Nielsen 1976) but has not yet proven practicable for routine operations because the small sampling rate (0.6 l/min.) results in a very low probability of encountering a plutonium-bearing particle. Virtual impaction techniques in which the larger particles are impacted at each stage into a slowly moving air stream, which is then filtered and counted, show promise and are about ten times as sensitive as the conventional alpha spectroscopy techniques developed in the early 1960s (Yule 1978; Loo, Jaklevic, and Goulding 1974).

Although the importance of particle size was recognized during the MED days, it was not until after the war that practical field instruments and techniques made their appearance (Stokinger and Laskin 1950). Prior to the development of the cascade impactor in the mid-1940s, impingers and electrostatic precipitation were the major instruments available, and these had serious limitations, not the least of which was varying and frequently unknown efficiency for different sized particles. The actual determination of size was also subject to gross errors and was commonly done by optical microscopy techniques.

The cascade impactor is a multistage sampling device that passes the air through a series of jets or orifices of continually decreasing size at right angles to each other (May 1945). Streamline design and the use of rectangular orifices produced high collection efficiencies for the various sized particles that were

(a) The plutonium-in-air monitor provides a clear illustration of technology transfer and how the development fruits of the government-funded national laboratories encouraged and spun off private industries: In 1967, Edgar Beard, a technician at what was then the Lawrence Radiation Laboratory at Livermore, left the Lab to form a company centered around the manufacture and sale of this device. Ironically, one of his first (and perhaps even his first) orders for the commercial version of this device came from another Atomic Energy Commission (AEC) laboratory. Over the years, RaDeCo, the company that Ed Beard initiated as a cottage industry, manufacturing the first units in his garage, made many improvements on the original device and expanded into other product lines as well, using many public-domain government developments. The history of RaDeCo is a typical American success story; the prosperous company was ultimately sold and is now a division of SAI Incorporated.

collected on oiled slides, deposition resulting from the inability of the particle to follow the tortuous movement of the airstream because of the high relative momentum of the particles and the low viscosity of the air. Several overlapping size distributions were obtained, which were determined by direct microscopic examination. The original model was quickly improved and adapted to field use (Sonkin 1946; Laskin 1946).

Multistage impactors, although a significant improvement over thermal precipitators, konimeters, and impinger and electrostatic precipitator methods, were not widely used, partly because of their inconvenience and potential inaccuracy and the high degree of skill required for their use. Practical improvement was sought through the use of two-stage rather than the typical four- to six-stage impactors. The importance of particle sizing was underscored in 1952 independently by Eisenbud and Davies, both of whom suggested the use of two-stage sampling devices for radioactive dusts (Eisenbud 1952; Davies 1952).^(a) In 1953, several new particle size devices were proposed. One of these was the Hexhlet, which was a horizontal elutriator followed by a filter that seemed to have appropriate sizing characteristics since it followed the theoretical penetration curve proposed by Davies (Wright 1954). Other two-stage devices were also proposed, several of which utilized a small cyclone as the first stage (Watson 1953; Harris and Eisenbud 1953) and another that used a preimpinger (May and Druett 1953). The improved cascade impactor enjoyed some popularity during the 1950s, and the May preimpinger device and midget cyclone were first employed in the late 1950s (Hyatt 1960). Subsequent applications have included various improved multistage impactors, which is the instrument of choice today for field studies of particle size (Healy 1970).

Another field method for continuous monitoring of airborne radioactive dusts was the moving filter air monitor (Kuper, Foster, and Bernstein 1950). This device made its appearance in the late 1940s and consisted of an electromechanical device designed to continuously advance a strip of filter paper across an aperture through which air was being drawn. The rate of movement was sufficiently slow—one inch per hour was typical—that a volume of several cubic meters of air was drawn through any given portion of the paper strip during its traversal of the aperture. After collection of the dust, the tape was then passed in front of one or more detectors. Thin end window G-M tubes were typically used for beta-gamma counting, and if alpha counting was also to be done, a ZnS scintillator was commonly used. Depending on the adjustment of the rate of advance of the tapes and other mechanical factors, counting was generally accomplished about a half hour to as much as eighteen hours after the sample was collected.

The moving filter air monitor provided certain advantages over a static constant air particulate sampler. The relatively short sampling time for any given part of the filter eliminated the problems associated with dust loading and build-up on the filter and ensured a relatively constant sampling rate. Background counts attributable to natural radioactivity in the air were minimized, which permitted a more rapid and sensitive analysis for artificially made radio-nuclides. By use of two or more sequential counters, decay data could be automatically obtained by comparison of the counts; the interval between the

(a) [It was planned that the two stages represent respirable and nonrespirable size ranges respectively, or particle sizes that would deposit preferentially in the upper respiratory tract or the lower respiratory tract.]

counts could be readily adjusted simply by varying the path length of the moving filter tape between the two detectors. Similarly, if both alpha and beta-gamma detectors were used, the alpha/beta ratio could be determined, and this information could be used to evaluate the natural radioactivity concentrations, including determining the radon/thoron ratio in air.

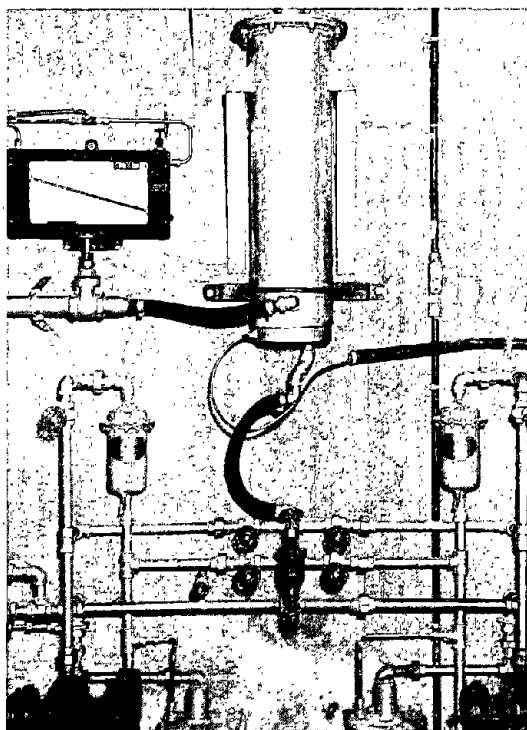
In the late 1950s, an interesting constant monitor for particulate radioactivity in air was developed that combined a moving paper filter tape assembly with an impactor (Hoy and Croley 1957). The theory behind this device was that large particles, such as those associated with uranium or plutonium, would be deposited on the filter paper while the smaller particles to which the natural radioactive daughters of radon and thoron attach would follow the air movement and not be collected. Thus, interference from natural background was eliminated. Although this relatively simple device did provide the desired separation of particles, it did not provide an accurate estimate of the hazard from internal emitters, as it did not adequately sample particles in the respirable range.

Initially, radioactive gases were sampled in the field by evacuated flasks, which were opened, usually by means of a stopcock, at the desired sampling location and returned to the laboratory for analysis (figure 18.3). An early field monitor for radioactive gases was described in 1951 and consisted of an evacuated 7.75-l Lucite ionization chamber coated with colloidal graphite (Aquadag) to make it conducting (Block 1951). Air was admitted to the chamber through a stopcock after first passing through a desiccant and a glass wool filter. After the sample was collected, the chamber was directly coupled to a quartz fiber electrometer, charged to zero on the electrometer scale, and the rate of drift timed and compared with a calibration curve made for the specific radionuclide under consideration. The apparatus was particularly applicable to low-energy beta-emitting gases such as tritium and ^{14}C .

Concern over airborne tritium hazards, coupled with increased use and by-product quantities of tritium, led to the development of continuous gas monitors for gaseous low-level beta emitters in the early 1950s (Kanne 1952; Driver 1956). These were largely flow-through ionization chambers, which were soon nicknamed "sniffers." In general, it was difficult to achieve adequate sensitivity with these instruments, unless a very large volume of air was collected, and very sensitive and delicate ammeters were used. Sniffers were also subject to spurious readings from ambient gamma radiation fields, dusts and other aerosols, humidity, and ions in air produced by cigarette smoke or by the passage of the air through the various orifices of the sampling system. Use of filters eliminated most of the problems associated with dusts, aerosols, and externally produced ions, and appropriate design of the sampling lines eliminated the internal ion production problem. Humidity effects were eliminated by a desiccant bed upstream of the sample chamber. Dual chambers—one sealed and one flow-through—were used to provide gamma compensation (Anthony 1959).

The low-sensitivity problem was to some extent solved by using as large a chamber as feasible; for a static device such as an effluent or room monitor, the chamber volume might be as large as 51.5 l, as was used in the Kanne chamber (figure 18.9), which dates back to MED days (Kanne 1952; Hoy 1961). Such large volumes were simply not feasible for portable instruments, not only because of their size but because of the size and weight of the associated air-moving equipment. A more practical chamber size of about 1 l permitted a lower level of detection of several MPCs; later improvements, particularly the advent of solid-state electronics and especially solid-state electrometers about 1960

FIGURE 18.9. A Kanne chamber (see text) installed on an effluent line. The manometer at left was used for flow determination; the piping underneath contains in-line filters for solids. (Photo courtesy of Pacific Northwest Laboratory.)



permitted detection of MPC levels with a high degree of reliability, and reduced the weight and increased the ruggedness of the instrument.

Development of field monitors for tritium and other gaseous radionuclides has been a continuous process, with many novel techniques tried, including concentric chambers (Osborne and Cowper 1966; Talbert 1975), solid scintillation detectors through which the air is passed after prefiltration or other pretreatment (Colmenares et al. 1974), and pulse height discrimination with proportional counters, a technique first developed as early as 1956 (Driver 1956).

Monitoring for plutonium and similar alpha emitters was initially accomplished by standard collection methods for particulates in air followed by alpha counting in the laboratory. Field detection and continuous monitoring of plutonium was revolutionized by the development of semiconductor detectors, which could be used for alpha spectrometry, permitting discrimination against radon daughters or other dust-borne alpha emitters. The first such units appeared about 1960 and permitted the detection of MPC levels of plutonium in workroom air within about eight hours (Phillips and Lindeken 1963). Instruments of this type have been the mainstay of field and in-plant monitoring for plutonium in air for more than two decades. The sensitivity limitation of these instruments is due in part to interference from ^{218}Po , a daughter of radon, which has an alpha energy close to that of ^{239}Pu —5.99 as compared with 5.15 MeV—and thus overlaps with or leaks counts into the plutonium channel. Because of the short half-life of the ^{218}Po , simple holdup can reduce the effect, but more sophisticated techniques such as lifetime analysis, made possible with microprocessor technology, can increase sensitivity by an order of magnitude, permitting detection of MPC levels of ^{239}Pu and other alpha emitters within thirty minutes (Kordas and Phelps 1979).

VI. Radon Monitoring and Working Level Meters

Monitoring of radon and daughters presents special problems and is inherently complicated by the state of equilibrium. In practice, measurements of radon

and daughters can be divided into three categories: (1) radon gas concentration; (2) radon daughter measurements; and (3) working level (WL) measurements.^(a) Radon daughter measurements are usually made with standard sampling instrumentation for airborne dusts followed by direct counting of the untreated sample. Beta counting may be accomplished after allowing the shorter-lived daughters to decay, by a back calculation of activity or concentration present at the time of sampling. Alternatively, alpha counting may be done. More sophisticated techniques involving alpha spectroscopy, determination of alpha/beta ratios or multiple counts at several times after the termination of sampling have also been used, with varying degrees of success. The great difficulty, of course, is the state of equilibrium between radon and its daughters at the time of collection.

As described earlier, early measurements of radon in the field were made on samples collected in evacuated flasks and measured with gold-leaf electroscopes or ionization chambers; calibration was made by comparison with a standard quantity of radon generated from a known amount of radium. Somewhat later, a technique was developed for purifying the radon collected in the flask and counting individual alpha particles, this being done in the laboratory (Curtiss and Davis 1943).

In the mid-1930s, a double ionization chamber method was developed (Evans 1935; Urry and Piggot 1941). One chamber was sealed and served to measure the ambient external radiation. The output from this chamber was used to offset the current from an identical chamber through which the air was passed, the readout of the net current being made with a string electrometer. Sensitivities in the picocurie range were easily obtained, although the operation of the device was somewhat temperamental and required a high degree of skill.

For thoron daughters, a portable ac-operated device was developed in the late 1930s in which the thoron daughters were collected on a brass disk carrying a negative potential of 3000 V (Evans and Goodman 1940). Although air was moved past the collecting disk, the measurement was independent of air flow and was based on counting the deposition of the long-half-lived (10.6-hr) thoron daughter. A proportional counter was also adapted to radon measurement by investigators at MIT (Brown, Elliott, and Evans 1942).

Direct measurement of airborne radon concentrations was improved considerably by the development of scintillation techniques. In the early 1950s, a continuous monitor using a ZnS(Ag) phosphor as the detector was developed by the AEC's New York Operations Office for continuous direct monitoring of airborne radon concentrations (Handloser 1959). Air, filtered to remove the radon daughters, was drawn into a sealed chamber containing a 3-in. diameter photomultiplier tube coated with the scintillation phosphor, the signal from which was fed into a battery-powered rate meter.

The scintillation technique was also adapted to grab sample analysis. In the mid-1950s, the Lucas cell was devised (Lucas 1957). This was simply a 200-ml chamber lined with ZnS(Ag) phosphor, which was exhausted prior to field use. In the field, a stopcock was opened to allow a sample of air to enter the chamber after passing through a filter to remove the dust-borne radon daughters. The scintillations produced by the alpha particles from decay of radon were determined directly with a photomultiplier, which viewed the walls of the

(a) [More in chapter 3.]

Lucas chamber through a clear flat window. This device, which has a sensitivity of about 10 pCi/L, has been widely used as a standard for more than twenty-five years.

An improvement on the Lucas cell was the so-called two-filter method, which utilized a standard air pump to pull air through a metal cylinder about 1 m long (Thomas and LeClare 1970). The cylinder was fitted with a filter at each end. Thus, the radon daughters present in the air being sampled were removed before entering the tube by the first filter, while the filter at the opposite end of the tube removed the daughters generated in the tube as the air was pulled through it. The alpha activity on the exit filter was counted in the field by means of a portable count rate survey meter utilizing a ZnS(Ag) detector. The detection threshold of this method was about an order of magnitude lower than that of the Lucas cell.

Working level measurements^(a) also began in the middle 1950s. The first and still widely used technique was the Kusnetz method, which used essentially standard and relatively simple air sampling instrumentation to collect a sample of dust from a known volume of air (Kusnetz 1956). The technique basically called for the collection of dust from 10 L of air at a flow rate of 2 L/min on a standard paper filter. Direct gross alpha counting of the filter was accomplished for 2 min after a standard delay time of 40 or 90 min; the WL was simply related to the gross alpha activity by a standard constant dependent on the decay time. The Kusnetz method and its many modifications provided an essentially instantaneous or spot sample and required only the use of ordinary air particle sampling and alpha counting equipment; the Kusnetz method was adopted as the American standard method for monitoring in uranium mines in 1973 (ANSI 1973).

The Kusnetz and similar rapid sampling and measurement techniques were lacking in that they were dependent to at least some extent on the degree of equilibrium between radon and its daughters and did not provide either continuous monitoring or a measure of the time integrated exposure to personnel. Moreover, the methods were slow in that a waiting period, commonly 40 min, was required before the analysis could be begun. For the standard Kusnetz method, a minimum of 47 min was required: 5 min to collect the initial sample, a 40-min delay time prior to counting, and a 2-min counting time. With setup time, an hour might typically be required to obtain a single measurement.

The difficulties inherent in the Kusnetz methods spurred development of instant working level meters, continuous monitors, and radon dosimeters by several groups, and over the years, several such devices have been created. Two so-called instant working level meters (IWLM) are relatively recent developments and utilize more complex measurement schemes than the Kusnetz or modified Kusnetz methods. Typically, IWLM devices are built around a surface barrier semiconductor for alpha-particle detection and may use spectroscopic techniques to distinguish between the alphas emitted by ^{218}Po and ^{214}Po . One such early IWLM was developed in 1972 and actually measured the concentrations of individual daughters from which the total alpha energy emitted and hence WL could be calculated (Groer, Evans, and Gordon 1973). This device uses three counting channels, two for alphas using semiconductor barrier detectors and a plastic scintillator for beta. Sampling is accomplished by drawing air through a moving paper tape for a 2-min period, which follows a 1-min

(a) See chapter 3 for details of the development and use of the working level concept.

background count. After sampling, a 2-min count is taken, and the WL is calculated electronically. Only 5 min are required for a measurement.

Only 2 min are required to obtain WL with a surface barrier detector device that measures ^{214}Po and ^{218}Po separately on a filter paper tape through which 1 l of air has been drawn with a hand pump (Schiager 1977). A somewhat earlier device used a surface barrier detector for a gross alpha count during the collection period and for a short period afterward (James and Strong 1973). Yet a different type of IWLM, based on total counts of alpha and beta activity, has also been developed (Shreve, Miller, and Cleveland 1977). All provide WL measurements within 5 min.

Integrating working level monitors actually chronologically preceded the instant working level monitor, with early versions appearing about 1970 (Schiager 1974). These units were based on the use of thermoluminescence dosimeters to integrate the alpha-particle output from dust collected on a filter. Such devices have been successfully used in uranium mines and mills as well as in other applications such as phosphate manufacturing.

Several interesting personnel monitoring devices have evolved in recent years. The radon film badge was invented in the mid-1960s and consisted of a sheet of alpha-sensitive photographic film in a specially designed light-tight holder that permitted entry of radon gas (Geiger 1967). Radon concentrations were determined by counting alpha-particle tracks on the developed film. Other passive personnel dosimeters based on track etch techniques also appeared or were tried about 1970 (Auxier et al. 1971; Lovett 1969; Rock, Lovett, and Nelson 1969), along with a Polaroid device (Bedrosian 1969) and a ZnS-film system (Costa-Ribeiro et al. 1969), thermoluminescence and thermally stimulated exoelectron emission (McCurdy, Schiager, and Flack 1969; Gammage, Kerr, and Huskey 1976), and cellulose nitrate plastic (Alter and Price 1972; Breslin 1977). Recently, active personal radon daughter dosimeters have been developed and appear to show promise (Durkin 1979; Parkinson, Roze, and Shepherd 1981). These devices basically contain a solid-state surface barrier detector and associated electronics including microprocessors to evaluate the counting data, along with a personal air sampler. In practice, air at a low flow rate is drawn through the sampler and deposited on a filter and directly examined by the detector. Sample counting and readout require about three hours, making this device faster than most passive dosimeters, although not as rapid as air-sampling and measurement techniques for determination of the WL. In general, the accuracy and reliability of these devices have been wanting, in particular when they are subjected to harsh mine environments (White 1969).

VII. Surface-Contamination Monitoring

Monitoring surface contamination in the field is vital to the control of radionuclide exposures but is an indirect and generally nonspecific measurement technique. From an internal hazard standpoint, monitoring of alpha surface contamination is of greater importance than monitoring for beta-photon emitters. Almost from the beginning of the MED, surface contamination was monitored in the field by portable survey meters of various types (Morgan 1947, 1950; Parker 1947, 1980) (see figures 18.10 and 18.11). Initially, these early instruments were equipped with gas-filled detectors. As the early state of the art did not permit practical manufacture of a Geiger tube with a window sufficiently thin to admit the short-range alpha particles, thin window unpressurized

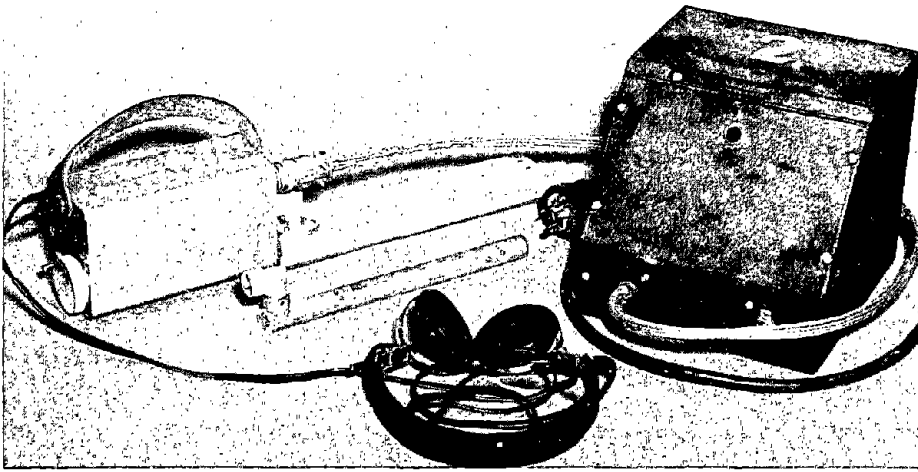


FIGURE 18.10. A portable “poppy” for alpha monitoring in the field, dating from before 1950, connected to a battery charger (right). The probe in the foreground was a BF_3 tube, permitting the same portable electronics package to be used for neutrons as well. (Photo courtesy of Pacific Northwest Laboratory.)



FIGURE 18.11. This array of portable monitoring instruments, from early post-Manhattan District days, shows how physical appearance accounted for the rather unusual names in the text. From left to right, the instruments are Bazooka, Portable Poppy, Cart Poppy, Soup Bowl, Cutie Pie, Totem Pole (a later version of the Fish Pole), and, finally, a plain old Geiger counter. The ladies with the Portable Poppy and Geiger counter are both wearing earphones. (Photo courtesy of Pacific Northwest Laboratory.)

ionization chambers and air proportional counters were used. Both types of detectors had disadvantages, including relatively low sensitivity, slow response time, and cantankerous response characteristics. Humid atmospheres would produce erratic response and arcing, particularly in proportional counters, and atmospheric pressure changes could significantly alter sensitivity and calibration factors.

A major problem plaguing the earlier attempts at field measurement of contamination was the general inadequacy and especially the instability of available power supplies. Available power supplies were subject to drift and could not provide the stability of voltage required for trouble-free operation. Thus, an instrument might work well at one site but not at another; an instrument suited to the dry thin air altitude of the Los Alamos mesa (5,000 ft +) might be totally unsatisfactory in the denser more humid air at Berkeley or Oak Ridge. In 1943, this problem was essentially solved by the development of a two-tube balanced circuit by H. L. Overbeck at Oak Ridge, which permitted the production of a power supply suitable to field use. The initial version of this circuit used a pair of 959 vacuum tubes, and the instrument it powered, the "Paint Pail," was relatively insensitive and therefore not useful as an alpha contamination monitor, although it was used for a time for external radiation surveys. Subsequent improvements to the circuit, including the use of a pair of CK 570 AX triodes, made possible the Zeus, a battery-powered ionization chamber survey meter that was used for surface contamination monitoring in the MED. The Zeus circuitry was basically a Wheatstone bridge in which two of the resistors were replaced by the plate resistance of the tubes. The alpha-, beta-, photon-detecting Zeus was subsequently improved by the addition of a feedback circuit, which provided greater sensitivity. This new instrument was named the Zeuto. Typical detection limits were two hundred disintegrations per minute.

At Hanford, the handheld portable air proportional counter was found to be unsatisfactory for in-plant use. In its place, a large ac-powered unit was developed, which featured a standard laboratory binary scaler-rate meter as the readout device in addition to a speaker that sounded clicks or pops to indicate each alpha count (see figures 18.7 and 18.12). Use of

FIGURE 18.12. Exiting an area with the potential for loose alpha contamination; the cart poppy will be used by the monitor at left. Note the radiation warning sign at right, which predates the current three-bladed warning sign adopted in the early 1950s. The sign was white with red lettering and borders. (Photo courtesy of Pacific Northwest Laboratory.)



ac current eliminated many of the problems related to the voltage instability and variability of the dc power supplies available at the time. The device was clearly too large and bulky to be hand carried; the scaler electronics—tube type with heavy iron core high-voltage transformers—weighed well in excess of twenty pounds. Thus, the unit was mounted in a specially designed three-wheeled metal cart with a large handle, allowing it to be moved from room to room or wherever it was needed. This venerable instrument, appropriately named the cart poppy after its popping speaker, served the needs of the Hanford Works for more than three decades. So well thought of was this device that as late as 1969, one operating manager attempted to order identical replacements for his aging original design units, voicing his belief that the instrument simply could not be improved upon. The unavailability of obsolete key components, including vacuum tubes, coupled with potential fabrication costs orders of magnitude greater than modern transistorized replacements, brought the old liner into the solid-state age. The modern replacements were a success, and perhaps thirty years hence identical replacements for them will be ordered by the spiritual descendants of users of the cart poppy.

Despite the drawbacks, the air proportional counter was a mainstay at many laboratories. For many years, Berkeley and Los Alamos favored the air proportional counter, using a handheld portable instrument with a 60-cm² area air proportional counter detector connected to a relatively large vacuum tube electronics package. Total weight of the unit was about two-hundred pounds, leading to the affectionate name of “Pee Wee” for the heavy bulky package. As electronics advances produced improved circuitry and in particular voltage regulators, portable air proportional counters of various types flourished. Another major advance occurred about 1955 with the practical production and application of wire with a diameter of 0.0005 in., which allowed better collection efficiency and more uniform fields in the detector, minimizing probe microphonics and other environmental effects.

At Hanford, the favored portable alpha monitor was the scintillation “poppy,” made possible by the development of the scintillation counter and especially photomultiplier tube advances during and shortly after World War II (Curran and Baker 1944; Kallman 1949; Coltman and Marshall 1947; Morton 1949) (see figure 18.8). The poppy converted the light flashes from a ZnS(Ag) scintillator into audible “pops,” one pop for each light flash. Initially, contamination levels were determined by counting the number of pops emitted by the instrument during a specified time period, which could be as short as 10 or 15 sec for relatively high levels and extended to a minute or two for very low levels. A proportional counter version of the poppy, developed at Oak Ridge (Borkowski and Marsh 1945), also was used for a time but could not compete effectively with the convenience and advantages of the alpha scintillator, which included stability, good rejection of beta and photon radiations, and typically greater sensitivity. Subsequently, a count rate meter was added, providing visible indication of the level of activity, but, at least at Hanford, the meterless instrument remained in use well into the 1960s. Scintillation detectors offered several advantages over gas-filled detectors, including greater sensitivity and much faster response time. They were not so dependent on highly stable power supplies and were unaffected by changes of humidity or pressure. They also produced a large signal, which could take advantage of relatively simple circuitry. They did, however, have a major drawback in that the photomultiplier tube was light sensitive and had to be kept in total darkness. Even a tiny pinhole in the

ZnS sheet covering the photocathode would admit enough light to produce high count rates and perhaps even damage the photomultiplier or at least render the instrument out of service for a period of hours.

The difficulties with the portable alpha instruments using gas-filled and scintillation detectors led to the development of a portable gas flow proportional counter by the Eberline Instrument Company in the late 1950s. This instrument was unaffected by environmental variables such as temperature and pressure and was equipped with a small pressurized bottle of counting gas. It was ideally suited to outdoor use where temperature and humidity changes might occur and was unaffected by pressure changes, since it maintained a constant flow of counting gas. Therein lay its drawbacks; the gas bottle ran dry after a few hours of operation and needed to be replaced; this was relatively expensive. In addition, the instrument was larger than the comparable scintillation or air proportional models because of the gas bottle "piggybacked" under the electronics package. Nonetheless, the instrument gained considerable acceptance. Gas flow could be checked visually in the field or elsewhere by igniting the gas streaming from the tiny outlet port of the detector. This made for a practical if not dramatic visual demonstration that the detector was operational and also permitted the gas flow to be adjusted appropriately by observing the size of the flame. It also was quite an attention-getter in operation; many a worker has done a quick double take at a health physics technician casually surveying a laboratory with a probe with a tiny blue flame emanating from its upper surface. Some more enterprising technicians, with a flair for the theatrical, would pretend to be searching for lost alpha particles that were visible only in blue light, or they would nonchalantly use the flame to light cigarettes when demonstrating the instrument outside of radiation areas. To date, there is no recorded instance of any accidental fires from these theatrics.

A key need in the early days of the MED was the detection of contamination on bench tops and similar flat surfaces, and for this purpose a box-like portable instrument with the detector opening on the bottom was built. This early instrument, named Juno, used a large ionization chamber as a detector. The chamber was equipped with a window thin enough to permit the entry of alpha particles and thus could be used as an alpha-contamination monitor, although it was relatively insensitive. Sliding shields—one plastic and one aluminum—could be used to cover the chamber window, permitting the instrument to be used as a beta-photon contamination monitor, or as a survey meter for external beta-photon radiation fields. The Juno was joined by the Samson (figure 18.13), an instrument of similar design and built for exclusive use as an alpha survey monitor;

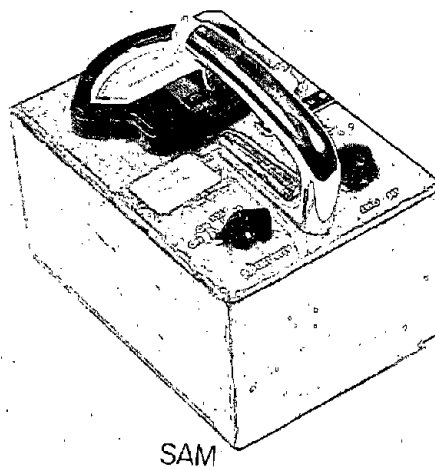


FIGURE 18.13. The Samson portable alpha meter. The chamber opening was underneath the instrument, making it convenient for monitoring surfaces. Note calibration graphs taped to the instrument. (Photo courtesy of Pacific Northwest Laboratory.)

its name may have been derived from the acronym SAM for standard alpha meter and the word son, as a second generation or "son" of the Juno. The Juno was among the first of the wartime instruments made commercially, and it proved to be remarkably venerable, still existent in the 1980s with modern MOS-FET (metal oxide silicon field effect transistor) and integrated circuitry in a physical configuration essentially identical to that of the first models.

Hand and shoe monitors, shoe monitors, and hand monitors also were developed in the MED and continue in use today, conceptually identical but far more sophisticated electronically (figure 18.14A, B). Portal monitors were also devised as a passive means of evaluating whether a person exiting a radiation zone

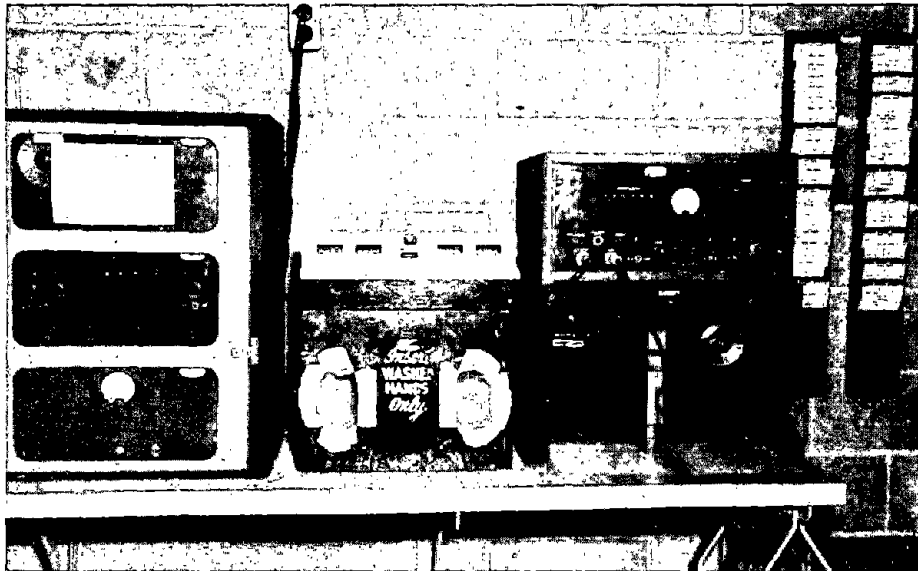


FIGURE 18.14A. (Above) An early portable hand monitor. Readout was provided by a binary scaler shown to the right of the detector; timer and register are mounted under the shelf supporting the scaler.

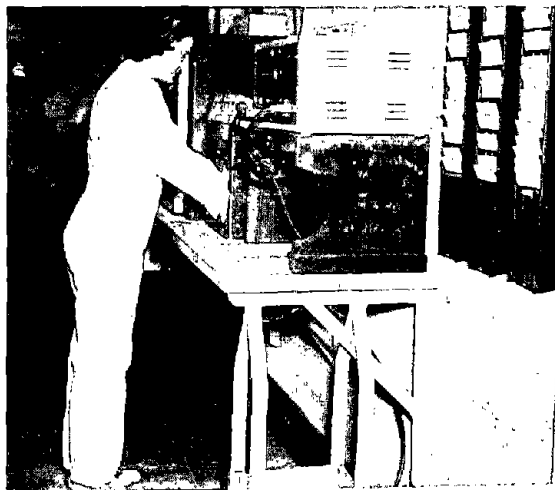


FIGURE 18.14B. (Left) The unit in use. Note saddle shoes, popular in 1940s, worn by user.

(Photos courtesy of R. L. Kathren and Pacific Northwest Laboratory.)

might be carrying radioactive contamination. The portal monitor consists of a door-sized opening framed by a number of detectors. As the individual passes through the opening, the contamination on (or in some cases in) the person will be detected. Typically, the individual would be required to pause in the portal for a time—perhaps as much as 90 sec, although from 10 to 30 sec was more common—to provide reasonable detection capability. Portals were (and are) typically narrow, to reduce the source-to-detector distance and improve detection capability. The more sophisticated models were designed to identify the detector that had the greatest count rate, which crudely localized the contamination. Other monitors, such as portal monitors and the walk-over monitor designed at the Savannah River Laboratory (Splichal 1972), were physically very large but achieved greater sensitivity and positive control in that personnel had to pass through the device in order to exit the facility. Floor monitors made their appearance in the 1940s, and basically were an adaptation of portable instruments to large-scale area monitoring. The Pee Wee was one of the many portable instruments adapted to this purpose.

The early portable instruments were tagged with a variety of often colorful, frequently obscure, and sometimes bizarre names (figure 18.11). To some extent, they reflected the security needs of the times, coupled with the perhaps wry sense of humor shown by the designers and users of the devices. Thus, to the Pee Wee already discussed can be added the Pluto, Juno, Sniffy, Samson, Chang and Eng, Paint Pail, Fish Pole, Bazooka, Giraffe, Zuto, Zeus, and, of course, the health physics mainstay, the Cutie Pie. Not all of these were useful for internal emitters; the Chang and Eng, for example, was a neutron survey meter with two identical appearing cylindrical chambers connected by a metal bar. The perhaps bizarre, but certainly fitting, name was derived from the famous Siamese twins of the Barnum and Bailey sideshows that excited an earlier generation.

The origins of many of these names are obscure; according to one source (Kathren 1975), the name Cutie Pie, now generically used to describe portable ionization chamber instruments, may have been derived from the fact that the response was a function of the charge (symbolized by physicists in mathematical expression as " Q ") and the geometry which was " 2π ." Hence, "Cutie Pie." Another story holds that the name was derived from the exclamation of a health physicist, who reportedly said "Isn't that a little cutie pie?" when he was shown the first prototype by the development engineers.

Important information regarding radionuclide contamination could often be inferred from measurements of external radiation fields, or sometimes inadvertently by instruments designed to measure external fields. An example of the latter is the film badge, which was typically worn by radiation workers in the MED and became, in fact, the ubiquitous symbol of the radiation worker. Contamination in the form of radioactive particles would sometimes settle or adhere to the badge, and when the enclosed film was developed, would appear as dark spots. This crude incidental autoradiography of contamination particles was quickly recognized by film badge technicians and utilized by operational health physicists to identify and control potential intakes of radioactivity. In the jargon, such films (and perhaps the wearers) were referred to as having measles because of the mottled appearance of a contaminated film, and the health physicist following up on a contaminated film incident was thus "investigating a case of measles."

Film badges were tried as early as the MED days for perimeter monitoring but, because of their inherent low sensitivity and susceptibility to environmental

damage, found little application. Both radiophotoluminescent and thermoluminescent dosimeters have been used with considerable success for external ambient measurements around nuclear facilities since the 1960s. One of the primary purposes of such dosimeters is to measure the external radiation fields in the environs of operating nuclear power plants, including the external radiations associated with the radionuclides and radiokryptons. The latter are primarily beta emitters, and dosimeters with a suitable "open window" and shielded area are necessary to gain quantitative information on the time-integrated release or concentration in terms of MPC-h of the noble gases.

Despite their great limitations, measurements of external photon fields have been used by operational health physicists since the earliest days of the MED to gain information on environmental contamination levels and the potential for internal exposure through intake of radionuclides. Geiger counters and scintillation chambers, because of their high sensitivity and fast response time, were ordinarily used for such purposes, although ionization chambers have been developed specifically for this purpose. Among the earliest applications of such instruments to protection from possible internal exposure were floor monitors, in which an array of several G-M tubes was suspended a few inches above the floor in a wheeled shielded housing. The readout ratemeter, electronics package, and operating controls were conveniently located at about waist height, enabling the operator to push the entire device along hallways and through various work areas, detecting contamination lying on the floor. Such instruments initially were designed and built by the various AEC sites, but by the mid-1950s, several commercial instruments of this type became available. Geiger-Müller and scintillation detectors were also mounted on vehicle bumpers and used for road or environmental area surveys. Portable Geiger counters and scintillators used in the field provided useful, albeit crude and primarily inferential, measurements of the hazard potential from internal radioactivity. They did, however, enjoy considerable vogue in uranium prospecting work, particularly during the 1950s.

A major limitation of both G-M counters and scintillators is photon energy dependence, which makes accurate measurements of environmental radiation levels difficult at best. This problem can be overcome by suitable response flattening filters, but these tend to reduce sensitivity and eliminate the all-important beta response. Although ionization chamber instruments have the disadvantage of poor sensitivity, one way of increasing sensitivity is with a pressurized ion chamber, thereby increasing the number of gas molecules in a given volume available for interaction. This requires special circuitry and led to the development of the Neher-White ionization chamber, originally developed in the 1940s by H. V. Neher and L. H. White. This device utilized an ionization chamber filled with pure argon at a pressure of 10 atm. With a chamber volume of only 50 cc, it was possible to measure over a range of six or seven decades. Despite their numerous limitations, including poor beta sensitivity and poor linearity of response, commercial portable survey meters featuring Neher-White circuitry and pressurized ionization chambers were popular for three decades and found wide application in fallout contamination monitoring associated with atmospheric weapons testing.

Cylindrical aluminum air ionization chambers with a volume of 40 l were used primarily at the Hanford site for a number of years to monitor ambient photon fields and to detect environmental contamination (Rising 1960). The ionization current was read out directly by a portable battery-powered

electrometer mounted atop the large volume chamber, which, because of its size and appearance was nicknamed the "milk can" by the calibration technicians and radiation monitors who used them in the field. The tube-type electrometers initially used were temperamental and not very rugged, and the units were upgraded with solid-state electrometers when these became available in the late 1950s.

More germane to internal emitter problems is the Pluto, a portable monitor for plutonium or other alpha-emitting surface contamination developed during the MED days. The instrument was named after Mickey Mouse's dog, Pluto, a very popular cartoon figure during World War II. The name, however, upset General Groves on security grounds because of its similarity to the then-secret element-plutonium. He thus decreed that the name should not be used, and for a time the instrument was renamed "Sandy" after Little Orphan Annie's dog in another popular cartoon strip of the time. Officially, the instrument was designated "Snoops," but, General Groves notwithstanding, the name Pluto stuck, and, along with the Sniffy, an appropriately named air sampling device, the Pluto was one of two health instruments named in the Smyth Report published immediately after the atomic bombings of Japan (Smyth 1945).

An interesting and highly effective device for monitoring plutonium contamination in the field under adverse environmental conditions was developed as a result of a military aircraft crash in 1964 near Palomares, Spain, involving nuclear weapons. Known by its acronym FIDLER (Field Instrument for Detection of Low Energy Radiation), this device used a thin scintillation detector and a two-channel pulse height analyzer set for 17 keV and 60 keV (the plutonium and ^{241}Am photons); it is capable of detecting plutonium contamination levels of a few hundred nanocuries per cubic meter over rugged uneven terrain (Tinney, Koch, and Schmidt 1969).

Portable battery-powered spectrometers for field application made their appearance about 1960, largely made possible by the advent of the transistor. One of the earliest commercial units was a single channel analyzer made in the configuration and size of a handheld survey meter by the Eberline Instrument Company. A later version of this unit featured two channels, and subsequent models made by Eberline and other manufacturers had special features such as hard-wired detection capability of the 364-keV photon associated with ^{131}I and scanning capability.

Although some water monitoring was done in the MED, the method used was simply immersion of detectors of various types into the liquid, useful only for fairly high concentrations of beta-photon emitters. Somewhat more sophisticated monitors were developed shortly after the war, using several thin side wall G-M counters to enhance sensitivity (Hursh, Zizzo, and Dahl 1951). Isotopic measurements of specific radionuclides in water were made in the field by ordinary gamma spectroscopy techniques. A combined alpha and beta-photon water monitor was made commercially as early as 1952, having both G-M and ZnS(Tl) detectors (AEC 1952). Systems have also been made for continuous measurement of tritium in water using a flow diversion-mixing technique and liquid scintillation counting.

VIII. In-Vivo Counting

In its simplest form, in-vivo counting could be accomplished by using a G-M survey meter to detect iodine in the thyroid if the activity levels were sufficiently

high (figure 18.15). Direct field measurement of internal emitters in vivo was accomplished by use of whole-body counters, which were made relatively lightweight and transportable and, hence, suitable for field use. Early whole-body counters were simply large shielded rooms; one such unit, developed at Brookhaven National Laboratory, weighed twenty-one tons and was transported by ship for use in fallout studies of the Marshallese (Cohn et al. 1963). Shadow-shield whole-body counters were pioneered at the Hanford Laboratories (Palmer and Roesch 1965) and made into portable truck-mounted units (Swanberg 1963; Brady and Swanberg 1965). A similar mobile whole-body counter was also developed in Sweden (Van Döbeln 1965). Although the sensitivity of these devices was initially not nearly as good as could be achieved in the laboratory using large shielded rooms with graded shields, for many applications, particularly for detection of fission products, these devices are more than adequate. In a typical unit, subjects would lie on their back on a cot or bed which was moved underneath a large NaI(Tl) crystal shielded overhead and on the sides by lead. Thus, a traverse of the body was obtained. The shadow-shield detector had a background as low as the large iron room systems, and weighed only five tons (Palmer and Roesch 1965). Thus, it could be loaded into a truck or even onto aircraft to make in-vivo field measurements and was used in studies of fallout in school children in the Hanford area and in Eskimos and Laplanders in the Arctic; and in the Marshall Islands (see chapter 12, which includes a photograph of one such unit). The modern successor to the original Hanford design is now commonly used at nuclear power plants to routinely monitor workers for internal exposure to fission products. The much more ponderous and sensitive non-portable (laboratory) versions of in-vivo counters are described in chapter 17. The transportable units described here are simply modifications of the larger laboratory versions.



FIGURE 18.15. Field measurement of radioiodine contamination in the thyroid during the 1940s. (Photo courtesy of Pacific Northwest Laboratory.)

Portable survey instruments were also used to detect possible internal contamination from radionuclides, particularly the radioiodines, which are relatively rapidly taken up and localized in the thyroid (figure 18.15). Routine contamination surveys, at least on one occasion, are known to have detected

accidental internal contamination from radioiodines.^(a) More recent and modern techniques include a "quickie" type counter, which combines features of the portal monitor, in-vivo counter, and sophisticated computer-based multi-channel analyzer to provide an indication of internal gamma-emitting nuclides within a few seconds, at levels considerably below the maximum permissible body burden.

IX. Summary and Commentary^(b)

As in all branches of science, progress in the field of radioactivity was linked closely to advances in instrumentation and methodology. For measurement of contamination with radionuclides, either in-plant or in the environment, it was necessary to develop light-weight and rugged instruments. The developments aimed primarily at plant and site monitoring and, later, general field use are reviewed briefly in this chapter. The principles are no different from those applied to laboratory instruments and described in chapter 17.

Portable instruments were used in the field quite early by the cosmic-ray physicists. Also, the needs for monitoring medical installations that were using radium or x-ray machines stimulated the development of so-called R-meters, film badges, and the like.

During the Manhattan Project days these basic instruments were adapted to the conditions and different energies in the plants and to measuring environmental contamination on- and offsite. Much had to be done to develop instruments that could measure alpha-particle contamination with reasonable accuracy and still be rugged and portable. Details, including the colorful code names given to many of these field and monitoring instruments, are in the chapter along with pictures of some. They also are listed in the capsule chronology.

There were, of course, some new or almost new developments in the earlier years that were of special importance to these applications. Among these were low-voltage Geiger-Müller tubes, the development of special materials and quenching gases suited to high radiation fields, and thinner and stronger windows for alpha counters.

(a) On a Friday afternoon in the spring of 1964, an alert health physicist at the Nevada Test Site correctly interpreted the results of a personnel contamination survey made with portable G-M survey meters by technicians on several individuals who were exiting from tunnelling re-entry following an underground nuclear detonation. The affected personnel all showed measurable closed window radiation levels localized in the vicinity of the neck. They had been wearing respiratory protection suitable for particulates but not radioiodines. The affected individuals were flown to Livermore, where they were met at the airport and escorted to the whole-body counter at Donner Laboratory by a Livermore health physicist and technician. The counting (by Donner personnel), which lasted until nearly midnight that evening and through the next day as well, revealed a mixture of five radioiodines (mass numbers 131 through 135) in the thyroids of the four affected individuals. The most seriously exposed had an estimated thyroid dose approaching a kilorad. This rather bizarre incident underscored the importance of in-vivo counting as an operational health physics tool and was an important factor in justification of the first whole-body counter at Livermore; it also sparked a data sheet in *Nucleonics* on the relative activity of the radioiodines as a function of time after fission.

(b) [This summary was written by J. N. Stannard and was not seen in advance by the chapter's author.]

Much of the field and monitoring methodology involved air sampling and, to a lesser degree, sampling of water and biota. Measurements in-vivo were less common until the later years. For air sampling, the techniques of industrial hygiene were adapted to obtaining samples suitable for measurements of radioactivity. Gradually these became continuous monitors, and they became important, not only for record-keeping, but to provide warnings of any breaks in the containment systems. Similarly, continuous monitors could be set up in the environment to transmit information on the presence of, and any changes in, outside contamination. The adaptation of air-sampling procedures to measurements of radon and its progeny in air is described (see also chapter 3).

The methods used for the collection of fallout from nuclear weapons tests are not described here since they were reviewed briefly in chapter 12. The radiation measuring instruments applied to the fallout once collected varied from in-situ measurements with field instruments such as those described here to transportation of the samples to the laboratory for preparation and analysis by laboratory instruments. For more than very rough measurements, radionuclides such as plutonium and the actinides required elaborate radiochemical separations prior to measurement. These important procedures have had to be given short shrift in this book, but they can be found in the cited literature.

Field measurements of external beta or beta-gamma radiation from fallout were routinely done by methods related to the in-plant and environmental monitoring procedures of the nuclear energy industry, with some special modifications. Special mention should be made of a fairly recent development—the FIDLER, a scintillation detector that can conveniently provide waist-height measurements of plutonium surface contamination. It can even be mounted in an aircraft and used to survey ground contamination. While precision is not equal to good in-situ measurements on the ground, and certainly not to laboratory measurements, this device can survey fairly large areas in a short time. Thus, areas of high activity can be spotted, and the ground crews can be directed to them.

For many years, portable radiation detection instruments were kept available in communities for use in case of a civil defense emergency. It should be clear from this chapter that the shelf-life of such instruments is short enough to require regular maintenance. Also, they cannot be trusted in untrained hands. Perhaps we can look forward to the future development of field instruments that are always at the ready and ridiculously simple to operate. With solid-state technology, thermoluminescence, and related developments, current field instruments are very light, small, and rugged, in sharp contrast to those available in the 1930s and 1940s.

References

- AEC. See Atomic Energy Commission.
- Ahearn, A. J. 1948. Conductivity pulses induced in single crystals of zinc sulfide by alpha-particle bombardment. *Phys. Rev.* 73:524.
- Ahearn, A. J. 1949. A search for crystals that exhibit conduction pulses under alpha-particle bombardment. *Phys. Rev.* 75:1966-67.
- Alaoglu, L. and N. M. Smith, Jr. 1938. Statistical theory of a scaling circuit. *Phys. Rev.* 53:832-37.
- Alter, H. W. and P. B. Price. 1972. U.S. Patent 3,665,194.
- American National Standards Institute. 1973. *Radiation protection in uranium mines*. ANSI N13.8. New York.

- ANSI. See American National Standards Institute.
- Anthony, J. D. 1959. Portable tritium monitor has gamma compensation. *Nucleonics* 17(4):110-14.
- Atomic Energy Commission. 1952. *Radiation instrument catalog*. RIB-8 (suppl. 1). Washington, D.C.
- Aub, J. C., R. D. Evans, L. H. Hempelmann, and H. S. Martland. 1952. The late effects of internally-deposited radioactive materials in man. *Medicine* 31:221-329.
- Auxier, J. A., K. Becker, E. M. Robinson, D. R. Johnson, R. H. Boyett, and C. H. Abner. 1971. A new radon progeny personnel dosimeter. *Health Phys.* 21:126-28.
- Bedrosian, P. H. 1969. Photographic technique for monitoring radon-222 and daughter products. *Health Phys.* 16:800-802.
- Block, S. 1951. A survey meter for soft betas in air. *Nucleonics* 8(4):51-54.
- Borkowski, C. J. and C. R. Marsh. 1945. Poppy-pulse type detector for alpha, beta, gamma and neutrons. AEC-D-2410. Washington, D.C.: U.S. Atomic Energy Commission.
- Brady, D. N. and F. W. Swanberg, Jr. 1965. The Hanford mobile whole-body counter. *Health Phys.* 11:1221-24.
- Breslin, A. J., ed. 1977. *Radon workshop February 1977*. HASL-325. New York: Health and Safety Laboratory.
- Brown, S. C., L. G. Elliott, and R. D. Evans. 1942. Detection of radon by means of a proportional counter. *Rev. Sci. Instr.* 13:147-51.
- Cantril, S. T. and H. M. Parker. 1945. Status of health and protection at the Hanford Engineer Works. Metallurgical Laboratory report CH-3570. Also in R. S. Stone 1951: *Industrial medicine on the plutonium project*, pp. 476-84. New York: McGraw-Hill.
- Cohn, S. H., R. A. Conard, E. A. Gusmano, and J. S. Robertson. 1963. Use of a portable whole-body counter to measure internal contamination in a fallout-exposed population. *Health Phys.* 9:15-23.
- Colmenares, C., E. G. Shapiro, P. E. Barry, and C. T. Prevo. 1974. Europium-doped, calcium fluoride scintillator system for low level tritium detection. *Nucl. Inst. Meth.* 114:277-89.
- Coltman, J. W. and F. H. Marshall. 1947. Some characteristics of the photo-multiplier radiation detector. *Phys. Rev. Second Series* 72:528.
- Costa-Ribeiro, C., J. Thomas, R. T. Drew, M. E. Wrenn, and M. Eisenbud. 1969. A radon detector suitable for personnel or area monitoring. *Health Phys.* 17:193-98.
- Crookes, W. 1903. *Proc. Royal Soc.* 81:405. [Cited in E. Rutherford 1904. *Radioactivity*, p. 127. Cambridge Univ. Press; also in R. J. Strutt 1904. *The Becquerel rays and the properties of radium*, pp. 81-83. London: Edward Arnold.]
- Curran, S. C. and W. R. Baker. 1944. *A photoelectric alpha particle detector*. MDDC-296. Washington, D.C.: U.S. Atomic Energy Commission.
- Curtiss, L. F. and F. J. Davis. 1943. A counting method for the determination of small amounts of Ra and of Rn. *J. Res. Natl. Bur. Standards* 31:181-95.
- Davies, C. N. 1952. Dust sampling and lung disease. *Br. J. Ind. Med.* 9:120-26.
- Drinker, P. and T. F. Hatch. 1947. *Industrial dust*. New York: McGraw-Hill.
- Driver, G. E. 1956. Tritium survey instruments. *Rev. Sci. Instr.* 27:300-303.
- Duffendack, O. S., H. Lifschutz, and M. M. Slawsky. 1937. Production, characteristics and reliability of Geiger-Müller counters. *Phys. Rev.* 52:1231-37.
- Durkin, J. 1979. Electronic daughter radon dosimetry. *Health Phys.* 37:757-64.
- Eccles, W. H. and F. W. Jordan. 1919. A trigger relay utilizing three-electrode thermionic vacuum tubes. *Radiat. Res. Rev.* 1:143-46. See also *Electrician* 83(1919):298.
- Eisenbud, M. 1952. Retention, distribution and elimination of inhaled particulates with particular reference to the evaluation of radiological risk. *Arch. Ind. Hyg. Occup. Med.* 6:214-25.
- Elmore, W. C. 1949. *Voltage amplifiers*. Chapter 3 in Elmore and Sands 1949, pp. 124-201.
- Elmore, W. C. and M. L. Sands. 1949. *Electronics: Experimental techniques*. New York: McGraw-Hill.
- Evans, R. D. 1935. Apparatus for the determination of minute quantities of radium, radon and thoron in solids, liquids and gases. *Rev. Sci. Instr.* 6:99-112.

- Evans, R. D. 1937. Radium poisoning II: The quantitative determination of the radium content and radium elimination rate of living persons. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* 37:368-78.
- Evans, R. D. 1980. Origin of standards for internal emitters. In *Health physics: A backward glance*, eds. R. L. Kathren and P. L. Ziemer, pp. 141-57. New York-Oxford: Pergamon Press.
- Evans, R. D. and C. Goodman. 1940. Determination of the thoron content of air and its bearing on lung cancer hazards in industry. *J. Ind. Hyg. Toxicol.* 22:89-99.
- Gammage, R. B., G. D. Kerr, and L. Huskey. 1976. Exploratory study of the use of TSEE dosimeters in radon monitoring. *Health Phys.* 30:145-47.
- Geiger, E. L. 1967. Radon film badge. *Health Phys.* 13:407-11.
- Gingrich, N. S., R. D. Evans, and H. E. Edgerton. 1936. A direct-reading counting rate meter for random pulses. *Rev. Sci. Instr.* 7:450-62.
- Groer, P. G., R. D. Evans, and D. A. Gordon. 1973. An instant working level meter for uranium mines. *Health Phys.* 24:387-95.
- Handloser, J. S. 1959. *Health physics instrumentation*, p. 70. New York: Pergamon Press.
- Harris, W. B. and M. Eisenbud. 1953. Dust sampler which simulates upper and lower lung deposition. *Arch. Ind. Hyg. Occup. Med.* 8:446-52.
- Healy, J. W. 1970. *Los Alamos handbook of radiation monitoring*. LA-4400. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Hoy, J. E. 1961. Operational experience with Kanne ionization chambers. *Health Phys.* 6:203-10.
- Hoy, J. E. and J. J. Croley, Jr. 1957. Annular kinetic impactor. *Am. Ind. Hyg. Assoc. J.* 18:312-14.
- Hursh, J. B., S. Zizzo, and A. H. Dahl. 1951. Survey meters for water monitoring. *Nucleonics* 9(5):C-16-C-20.
- Hyatt, E. C. 1960. *A study of two-stage air samplers designed to simulate the upper and lower respiratory tract*. LA-2440. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- James, A. C. and J. C. Strong. 1973. A radon daughter monitor for use in mines. In *Proceedings of the 3d international congress of the International Radiation Protection Association*, ed., W. S. Snyder, CONF-730907, pp. 932-38. Held in Washington, D.C., September 9-14, 1973. Oak Ridge, Tenn.: Technical Information Center.
- Kallmann, H. 1949. Quantitative measurements with scintillation counters. *Phys. Rev.* 75:623-26.
- Kanne, W. R. 1952. U.S. Patent 2,599,922, June 10, 1952; filed October 12, 1944.
- Kathren, R. L. 1975. On the etymology of "Cutie Pie." *Health Phys.* 28:487.
- Kathren, R. L. 1980. Before transistors, IC's and all those other good things: The first fifty years of radiation monitoring instrumentation. In *Health physics: A backward glance*, eds. R. L. Kathren and P. L. Ziemer, pp. 73-93. New York-Oxford: Pergamon Press.
- Kip, A. F., A. G. Bousquet, R. D. Evans, and W. N. Tuttle. 1946. Design and operation of an improved counting-rate meter. *Rev. Sci. Instrum.* 17:323-33; and Erratum: Design and operation of an improved counting-rate meter. *Rev. Sci. Instrum.* 17:515.
- Kip, A. F. and R. D. Evans. 1941. Improved counting rate meter for radioactivity detection. *Phys. Rev.* 59:920.
- Kordas, J. F. and P. L. Phelps. 1979. A review of measurement techniques for stack monitoring of long-lived alpha emitters. *IEEE Trans. Nucl. Sci.* NS-26(1):757-64.
- Krebs, A. T. 1955. Early history of the scintillation counter. *Science* 122:17-18.
- Kuper, J. B. H., E. H. Foster, and W. Bernstein. 1950. Monitor for radioactive dust. *Nucleonics* 6(4):44-47.
- Kusnetz, H. L. 1956. Radon daughters in mine atmospheres—A field method for determining concentrations. *Am. Ind. Hyg. Assoc. J.* 17:85-88.
- Laskin, S. 1946. Modified cascade impactor. MDCC-1500, declassified December 1, 1947. Washington, D.C.: U.S. Atomic Energy Commission.
- Lewis, W. B. 1943. *Electrical counting*. Cambridge, England: Cambridge Univ. Press.

- Lindeken, C. L. and W. A. Phillips. 1961. Plutonium alpha air monitor using a solid state detector. In *Hazards control quarterly report no. 6*, July-September 1961, UCRL-6658, pp. 1-6. Washington, D.C.: U.S. Atomic Energy Commission.
- Loo, B. W., J. M. Jaklevic, and F. S. Goulding. 1974. *Dichotomous virtual impactors for large scale monitoring of airborne particulate matter*. LBL-3584. Berkeley, Calif.: Lawrence Berkeley Laboratory.
- Lovett, D. B. 1969. Track etch detectors for alpha exposure estimation. *Health Phys.* 16:623-28.
- Lucas, H. F. 1957. Improved low-level alpha-scintillation counter for radon. *Rev. Sci. Instrum.* 28:680-83.
- May, K. R. 1945. The cascade impactor: An instrument for sampling coarse aerosols. *J. Sci. Instrum.* 22:187-95.
- May, K. R. and H. A. Druett. 1953. The pre-impinger: A selective aerosol sampler. *Br. J. Ind. Med.* 10:142-51.
- McCurdy, D. E., K. J. Schiager, and E. D. Flack. 1969. Thermoluminescent dosimetry for personal monitoring of uranium miners. *Health Phys.* 17:415-22.
- Morgan, K. Z. 1947. Health physics and its control of radiation exposures at Clinton National Laboratory. *Chem. Eng. News* 25:3794-98.
- Morgan, K. Z. 1948. Radiation safety measures in an atomic-energy plant. *Eng. J.* 31:154-61, 166.
- Morgan, K. Z. 1949. Instrumentation in the field of health physics. *Proc. Inst. Rad. Eng.* 37:74-82.
- Morgan, K. Z. 1950. *Radiation protection in medical physics*, ed. O. Glasser, vol. 2, pp. 766-73. New York: Year Book Publishers.
- Morris, J. P. 1938. Hazards in the radium and mesothorium refining plant at the University of Missouri. *J. Ind. Hyg. Toxicol.* 20:36-45.
- Morton, G. A. 1949. Photomultipliers for scintillation counting. *RCA Rev.* 10:525.
- Nickson, J. J. 1951. *Industrial medicine on the plutonium project*, ed. R. S. Stone, pp. 75-112. New York: McGraw-Hill.
- Nielsen, J. M. 1976. *Pacific Northwest Laboratory annual report for 1975 to the ERDA Division of Biomedical and Environmental Research, Part 4, Physical and analytical sciences and analysis and assessment*. BNWL-2000, pt. 4. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Nucleonics Staff. 1948. Decade scaler. *Nucleonics* 2(1):84.
- Osborne, R. V. and G. Cowper. 1966. *The detection of tritium in air*. AECL-2604. Chalk River, Ontario, Canada: Atomic Energy of Canada.
- Palmer, H. E. and W. C. Roesch. 1965. A shadow shield whole-body counter. *Health Phys.* 11:1213-19.
- Parker, H. M. 1947 and 1980. *Health physics. Instrumentation and radiation protection*. MDDC-783. Washington, D.C.: U.S. Atomic Energy Commission. Reprinted as a landmark paper in *Health Phys.* 38:957-96.
- Parkinson, R. N., V. Roze, and R. Shepherd. 1981. The development and underground testing of the alpha dosimeter—A solid-state electronic personal radiation dosimeter for uranium miners. In *Radiation hazards in mining: Control, measurement, and medical aspects*, ed. M. Gomez, pp. 428-38. An international conference held at the Colorado School of Mines, Golden, Colo., October 4-9, 1981. New York: Society of Mining Engineers, American Institute of Mining, Metallurgical, and Petroleum Engineers.
- Pfahler, G. E. 1922. The effects of x-rays and radium on the blood and general health of radiologists. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* 9:647-56.
- Phillips, W. A. and C. L. Lindeken. 1963. Plutonium alpha air monitor using a solid state detector. *Health Phys.* 9:299-303.
- Quimby, E. H. 1926. A method for the study of scattered and secondary radiation in x-ray and radium laboratories. *Radiology* 7:211-17.
- Rising, F. W. 1960. *A portable dose rate instrument for measurement of natural background radiation levels*. HW-67787. Richland, Wash.: Hanford Works.
- Rock, R. L., D. B. Lovett, and S. C. Nelson. 1969. Radon-daughter exposure measurement with track etch films. *Health Phys.* 16:617-21.

- Rossi, B. and H. H. Staub. 1949. *Ionization chambers and counters: Experimental techniques*. New York: McGraw-Hill.
- Sands, M. L. and W. C. Elmore. 1949. *Electronic counters*. Chapter 4, pp. 202-79.
- Schiager, K. J. 1974. Integrating radon progeny air sampler. *Am. Ind. Hyg. Assoc. J.* 35:165-74.
- Schiager, K. J. 1977. The 3R-WL working level survey meter. *Health Phys.* 33:595-604.
- Schiff, L. I. 1936. Statistical analysis of counter data. *Phys. Rev.* 50:88-96.
- Schiff, L. I. and R. D. Evans. 1936. Statistical analysis of the counting rate meter. *Rev. Sci. Instrum.* 7:456-62.
- Schulte, H. F. and E. C. Hyatt. 1954. *Air sampling*. LA-1835, pp. 59-70. Los Alamos, N. Mex.: Los Alamos Scientific Laboratory.
- Shepherd, W. G. and R. O. Haxby. 1936. A scale of eight impulse counter. *Rev. Sci. Instrum.* 7:425-26.
- Shreve, J. D., Jr., R. W. Miller, and J. E. Cleveland. 1977. A new instrument for quick determination of radon and radon-daughter concentrations in air. Concept, analytical basis, calibration caveats, the embodiment and field results. In *Recueil des communications—Proceedings*, vol. 1, pp. 111-15. Proceedings of the 4th international congress of the IRPA held in Paris, April 24-30, 1977. Paris: International Radiation Protection Association.
- Smyth, H. D. 1945. *Atomic energy for military purposes*. Princeton, N.J.: Princeton Univ. Press.
- Sonkin, L. S. 1946. A modified cascade impactor: A device for sampling and sizing aerosols of particles below one micron in diameter. *J. Ind. Hyg. Toxicol.* 28:269-72.
- Splichal, W. F., Jr. 1972. Walk-over monitor for alpha and beta-gamma contamination. In *Health physics operational monitoring*, vol. 2, eds. C. A. Willis and J. S. Handloser, pp. 911-24. New York: Gordon & Breach.
- Stokinger, H. E. and S. Laskin. 1950. Air pollution and the particle-size toxicity problem—II. *Nucleonics* 6(3):15-31.
- Swanberg, F., Jr. 1963. *The Hanford mobile whole body counter*. HW-80216. Richland, Wash.: Hanford Atomic Products Operation.
- Talbert, R. A. 1975. A monitor for tritium in air containing other beta emitters. In *Proceedings of the 23d conference, Remote Systems Technology*. Washington, D.C.: American Nuclear Society.
- Taylor, L. S. 1967. An early portable radiation survey meter. *Health Phys.* 13:1347-48.
- Terry, R. D. 1980. Historical development of commercial health physics instrumentation. In *Health physics: A backward glance*, eds. R. L. Kathren and P. L. Ziemer, pp. 159-65. New York-Oxford: Pergamon Press.
- Thomas, J. W. and P. C. LeClare. 1970. A study of the two-filter method for radon-222. *Health Phys.* 18:113-22.
- Tinney, J. F., J. J. Koch, and C. T. Schmidt. 1969. Plutonium survey with an x-ray sensitive detector. UCRL-71362. Livermore, Calif.: Lawrence Radiation Laboratory.
- Urry, W. D. and C. S. Piggot. 1941. Apparatus for determination of small quantities of radium. *Am. J. Sci.* 239:633-57.
- Van Döbeln, W. 1965. A mobile whole-body counter. In *Radioactivity in man*, eds. G. R. Meneely and S. M. Linde, pp. 25-26. Springfield, Ill.: Charles C. Thomas.
- Victoreen, J. A. 1944. Roentgen rays: Measurement of quality by thimble chambers. In *Medical physics*, ed. O. Glasser, vol. 1, pp. 1370-82. New York: Year Book Publishers.
- Watson, H. H. 1953. Dust sampling to simulate the human lung. *Br. J. Ind. Med.* 10:93-100.
- White, O., Jr. 1969. An evaluation of six radon dosimeters. [For internal distribution only.] HASL-TM-69-23. Washington, D.C.: U.S. Atomic Energy Commission.
- Wright, B. M. 1954. A size-selecting sampler for airborne dust. *Br. J. Ind. Med.* 11:284-88.
- Wynn-Williams, C. E. 1932. A thyratron 'scale of two' automatic counter. *Proc. Royal Soc. (London)* A136:312.
- Yule, T. J. 1978. An on-line monitor for alpha-emitting aerosols. *IEEE Trans. Nucl. Sci.* NS-25(1):762-66.

Preface to Section VI

Therapy and Nuclear Medicine

The two chapters in this section are as close to clinical medicine and associated pharmacology as we will get in this compendium.

At several points in earlier chapters, e.g., radium (chapter 1), actinides (chapter 7), experience with fallout (chapter 12), we alluded to or briefly described approaches to the therapeutic removal of deposited radionuclides from the body, or prevention of their absorption. Actually, the subject was in the investigators' minds throughout the research and industrial experiences recounted. Since a body or tissue burden of a radionuclide cannot be turned off like an x-ray machine or other source of external radiation, the only recourses are to prevent or delay absorption or hasten elimination. The same problems concerned many in the field of chemical toxicology, especially the deposition and removal of heavy metals such as lead. Pharmacologists were busy trying methods and synthesizing chemicals that would, they hoped, complex with heavy metals and bring about the desired effects. This began even before World War II. Much effort was also devoted to developing antagonists for war gases. These activities were picked up by those interested in possible therapeutic removal of radionuclides. Small, but active, research groups pressed the investigations, and, before long, clinical trials were being started. Thus, there was both active research into the compounds and their effects in animals, as well as pressures to check out the results in humans. The possible need, should an emergency arise, was strong motivation for clinicians attached to the organizations handling radionuclides in quantity. As a result, this is one area where the conventional pharmacologist-toxicologists and representatives of the internal emitter establishment worked quite closely.

Chapter 19 reviews the early experimental approaches to therapeutic procedures, the development of chelators and chelation therapy, the active experimental programs, and briefly, the experience in humans. Because the work was in many respects more strongly developed in European laboratories than in the United States, the chapter has more review of work done abroad than many chapters in this book. What it does not say is that chelation therapy has, despite the problems noted in the chapter, become a more or less standard form of potential treatment. Nearly every installation where human beings handle reasonably large quantities of radionuclides has the means for chelation therapy in stand-by form in its medical department.

In chapter 5, we saw the beginnings of the use of radioisotopes for diagnosis and therapy that were later called nuclear medicine. In chapter 6, we saw that therapeutic uses were on the minds of investigators at Berkeley when they were deflected by more urgent problems. Even during the war years, these possibilities were not forgotten; indeed, some progress was made as the accelerators became more powerful and the nuclear reactor began to supply radionuclides in quantity. At the end of the war, many clinicians who had been sequestered by war work were anxious to make use of the potentials revealed, and nuclear medicine took off on an expansion that has hardly slowed at all ever since. Chapter 20 reviews the aspects of nuclear medicine with direct bearing on the theme of this book—the health effects of radionuclides.

For obvious reasons, the detailed clinical aspects of nuclear medicine procedures are far too extensive for more than a glimpse in chapter 20. Imaging and other diagnostic aspects had to be given short shrift. Yet, there is enough to convey the fundamental nature of the operations. Uses in therapy receive more attention, for here we are dealing with a direct health effect of the radionuclide. Also, much emphasis is placed upon a central theme of nuclear medicine, viz., the extraction of maximum diagnostic information with minimal radiation dose to the patient, or maximum therapeutic effect in the target tissue or organ, with minimal effects on other nontarget tissues or organs.

Dosimetry of internal emitters receives formal discussion in chapter 20. Obviously, the principles of such dosimetry have had to be appreciated at many earlier points in our discussions. However, it seemed wise to put off formal presentation until both the “conventional” system and the one developed by the Medical Internal Radiation Dose Committee (MIRD) of the Society for Nuclear Medicine could be discussed together. (The reader was warned of this delay in the general preface.)

Chapter 20 ends with some gratuitous remarks on possible extensions of current trends in therapy that may or may not develop in the future. Nuclear medicine is such a rapidly developing field that one is emboldened to make prophecies!

It might be thought that financial support and manpower for nuclear medicine would be far less associated with the activities of government than many other areas we have reviewed. This is now true. Yet, in the formative years, the field got much of its impetus and some of its support from the agencies we have become familiar with in earlier sections. Even organized medicine, strong as it now is, could not or would not have supported the construction and operation of the accelerators that produced the radionuclides that gave nuclear medicine its start. This is even more true of the extensive program for distribution of radionuclides from nuclear reactors for cancer research and therapy and other biomedical uses begun under the Atoms-for-Peace program, probably its most durable contribution to posterity.

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Capsule Chronology

- 1926 Deleading procedures proposed and tried, mostly by manipulation of calcium metabolism (Aub, Evans, et al., Massachusetts General Hospital and MIT).^(a)
- 1927 Viosterol and parathyroid extract considered for deleading.
- 1929 Parathyroid hormone used for therapy of radium poisoning (Flinn and Sedlin, John Hopkins).
- 1931 Viosterol used for above (Flinn).
- 1935 Dietary calcium changes tried for removal of radium (Craver and Schlundt).
- 1938 Deleading treatments outlined above applied to patients and animals with body burdens of radium (Aub et al., Massachusetts General Hospital and MIT).
- 1942 First suggestion of use of a complexing agent for decorporation of heavy metals (Kety).
- 1945 Importance of complexing emphasized in all work with deposited radionuclides (especially Neuman et al. at Rochester; Schubert, Met Lab).

Development of British anti-lewisite (BAL) for treatment of chemical warfare agent effects, e.g., lewisite; leads to ideas for decorporation of heavy metals (Peters and others, United Kingdom).
- 1946 Berkeley works hard on factors influencing absorption and retention—cathartics, low- and high-calcium diets, etc. Tried for strontium, yttrium, cesium, and plutonium.

Chicago work on effects of sodium citrate and related complexers on excretion of plutonium in animals (Paintér).
- 1947 Idea of metal displacement advanced by Schubert (Chicago). Uses zirconium. Also considerable expansion of work on sodium citrate.
- 1948 BAL does not work for uranium (Neuman and Allen at Rochester).

Toxicity of zirconium reported to be low in rats (McClinton and Schubert, Argonne).
- 1949 Zirconium administration tried for plutonium and yttrium in animals (Schubert, White, and colleagues, Argonne).

Hursh shows increased removal of polonium in rats by BAL (Rochester). Also 1952.
- 1950 First test of EDTA for removal of a radionuclide, viz., plutonium (Foreman, Berkeley). Also general reports on chelation work at Berkeley (Foreman).

BAL only moderately successful for thorium.
- 1950s Hanford begins work on removal of inhaled radionuclides; continues for many years (Tombropoulos and Bair).

(a) For abbreviations and acronyms, see Appendix D.

- 1950s** Use of complexers and chelators for treatment of wounds at Hanford reviewed.
- Chelation chemistry advances rapidly, and chelators are tried in many laboratories.
- Various physiological variables tried.
- Experimental work begins on uses of chelating agents in humans.
- 1951** Report of radiostrontium metabolism and decontamination in man (Laszlo and Spencer at New York).
- Trial of BAL for removal of ^{32}P and ^{90}Sr ; not effective (Kisilefski et al., Argonne).
- 1952** Hursh demonstrates changes in tissue distribution of polonium after BAL (Rochester).
- First description of toxicity of chelators.
- 1953** Detailed work on nature and importance of citrate complexes with uranium (Feldman and Neuman at Rochester).
- Early Los Alamos work on chelating agents (Foreman).
- Work on zirconium begins at Hanford (Temple, Wager, Joffe, and Thompson).
- 1953-1965** Several reviews by Foreman on pharmacology of chelators.
- 1954** Sodium and calcium-EDTA compared and latter preferred (Foreman, Los Alamos).
- Early joint Hanford-Los Alamos reports on chelation trials in man (Foreman, Fuqua, and Norwood).
- Trials of BAL for removal of plutonium not successful (Kawin and Copp, Berkeley).
- Hursh demonstrates that BAL reduces toxicity of polonium in rats.
- 1955** EDTA kept ready at Hanford for possible use in accident cases (Norwood).
- Zirconium used in human contamination case at Hanford (Norwood).
- Mid-1950s** Trials of DTPA and EDTA in man begin at Hanford and Los Alamos.
- Becoming evident that zirconium action is a carrier effect, not a metal displacement, and is limited to circulating radionuclides.
- Idea advanced that zinc removal may underlie toxicity of chelators (Schroeder).
- 1956** Americium exposure case at Berkeley treated with Ca-EDTA (Dobson).
- Ca-EDTA tried at Argonne in ^{227}Th wound case.
- Rosenthal edits AEC general report on therapy of radionuclide poisoning (Argonne).
- Ionophoresis tried for skin decontamination (Michon, France).
- Berkeley group tries zirconium for removal of yttrium (Copp and Kawin).

- 1956** NRDL tries zirconium (Cohn et al.).
MacDonald (UCLA) declares medical armamentarium for radiostrontium removal is lamentable.
Kidney damage reported in a few patients receiving DTPA (Foreman and Lushbaugh, Los Alamos).
- 1957** Zirconium used on two cases in the United Kingdom. Side effect of serious labyrinthitis in both cases causes much concern and essentially cuts off further use of zirconium therapy in humans.
Ultrasonic methods tried at Hanford (Neef and Ballou).
- 1960** Book by Seven and Johnson on metal binding in medicine is a landmark for the field.
Reports of nephrotoxicity of some chelators. Schroeder reviews pharmacology of chelators.
- 1960s** Extensive animal work with EDTA, DTPA, DFOA, and other chelators done for removal of transuranics in animals (Taylor, U.K.; Fried, Schubert, Rosenthal, Lindenbaum, Argonne; Smith and colleagues, Battelle; Belyaev, USSR; Seidel, Volf, FRG; Lloyd et al., Utah; Cohen et al., NYU).
Potentially lower toxicity of Zn-DTPA indicated by Norwood (Hanford).
Miscellaneous substances tried for removal of radiostrontium. Reviewed by Nelson (United Kingdom) in 1963.
Much work by Spencer and colleagues on metabolism of tracer levels of many radionuclides in man. Chelated forms compared to ionic forms.
Hypocalcemia with chelators reviewed (Seven).
Spencer reviews experimental work on radiostrontium removal in man.
- 1961** Diuresis and diuretics tried for removal of radiocesium.
Chelating agents tried for removal of thorium (Fried and Schubert, Argonne).
- 1962** Several human cases at Hanford described at symposium on Biology of the Transuranic Elements. DTPA substituted for EDTA. Decorporation as effective in man as in animals.
IAEA meeting on diagnosis and treatment of radioactive poisoning.
Work on removal of inhaled radionuclides at Hanford reported (Tombropoulos and Bair).
Catsch addresses general principles of chemistry and pharmacology of chelators.
- 1962 et seq.** Search continues for effective oral chelating agent (Ballou, Hanford).
- 1963** French experience described for DTPA in wounds (Lafuma).
Use of chelators in the Marshall Islands from 1955 on, described by Cohn (Brookhaven).
Volf on treatment of radiostrontium uptake in man.

- 1963 Prophylactic and therapeutic measures described in Hanford symposium on radioiodine.
Several agents tried for ruthenium removal (Catsch et al.).
Plurionics tried at Hanford; other surface-active agents, also extensive cadre of parasympathetic drugs.
- 1964 Schubert reviews pharmacology of chelators.
Iron complexers tried (Keberle).
Chelators do only moderately well for removal of inhaled radionuclides (Hanford).
Lovelace Laboratory enters studies of removal of radionuclides from lung.
Idea proposed of adding inert agents to increase lung elimination rates (LaBelle, Rochester-Jefferson). Effect small.
- 1965 Early Rocky Flats reports.
- 1966 Review of Rocky Flats contamination cases, mostly wounds, and the therapies used (Piltingsrud).
European work on Prussian blue in man.
- 1968 Reports of attempts to change gut absorption in man; extend over many years.
Alginates tried for same purpose in animals (Stara and colleagues, USPHS).
Schulte and Whipple (Los Alamos) question use of chelators.
- 1968-1969 Lung lavage tested for removal of plutonium from animal lungs (Sanders, PNL; Pflieger, Lovelace).
- 1969 Methods for reducing gut absorption reviewed by Bair and Smith (PNL).
Zymosan tried for increasing phagocytic removal of ^{137}Cs in fused clay (Thomas et al., Lovelace).
Dosage regimens for chelation compared (Rosenthal et al., Argonne).
- 1970 Work on promethium in man (Palmer and Nelson, PNL).
- 1970-1974 Work at Fontenay-aux-Roses on treatment of intramuscularly injected transuranium elements (Nénot, Morin, et al.).
- 1970s Much work in Europe on relative toxicity of Zn-DTPA versus Ca-EDTA.
Series of reports from Lovelace of use of pulmonary lavage (Muggenburg et al.).
Much work at Utah on toxicity of chelators to embryo and fetus.
Case of americium contamination of long standing (began in 1963) found in Albany, New York. First published findings in 1972. Father and son exposed. Therapy with DTPA continued periodically through 1975. Measurements continue (Cohen, Wrenn, and colleagues, NYU) for several years.
- 1972 Pulmonary lavage used on human case contaminated with plutonium (McClellan et al., Lovelace).

- 1972** Small nebulizers developed for giving chelators as aerosols (Smith, PNL; Jolly, Savannah River).
Lovelace reports on intravenous DTPA for removal of inhaled materials (Pfleger and colleagues).
Ca-DTPA causes a transient inhibition of DNA synthesis; Zn-DTPA does not (Taylor et al., United Kingdom).
- 1973** Review of Hanford-Battelle inhalation and wound cases from 1946 through 1971 (Parker).
Review of DTPA effects on removal of trivalent actinides (Durbin, Berkeley).
Reduced absorption of radiostrontium with sodium alginate reported (Borisov, USSR).
Ferri-ferrocyanide tried for removal of radiorubidium (Richmond, Los Alamos).
Glucan \pm DTPA tried for removal of plutonium from liver (Rosenthal et al., Argonne).
Work begins at Battelle on pulmonary toxicity of chelators (Smith, Ballou, and colleagues).
- 1974** Lethality of large doses of Ca-EDTA attributed to removal of zinc.
- Mid-1970s** Utah group enters chelation therapy field in earnest (Calder, Lloyd, Mays). Zn-DTPA considered more effective than Ca-EDTA for long-term use and less toxic.
- 1975** Review of therapy of sixteen human cases, primarily wounds, by Dolphin (United Kingdom).
French work on pulmonary lavage. Able to lavage both lungs at single sitting (Nolibé).
- 1976** Catsch shows that margin of safety is narrower for continually maintained blood levels of Ca-DTPA than for single or spaced doses.
Utah reports on Ca-DTPA and Zn-DTPA for removal of americium.
Cohen (NYU) compares americium metabolism and effects of therapy in man to that in baboons.
- 1977** Some measurements made of reduction of effects in animals treated by pulmonary lavage (Muggenburg, Lovelace).
- 1978** Fifty-four human cases summarized by Volf (FRG).
Comprehensive review, also by Volf, published by WHO-IAEA.
Mixed ligand therapy described (Schubert). Subsequently proven ineffective.
- 1979** Lavage favored as most effective method for removing inhaled long-lived radionuclides (Muggenburg, Lovelace).
Seventh edition of Albert's book on selective toxicity reviews chemistry of chelators and chelation and broad applications of these agents.

- 1979 Argonne work on chelation of plutonium in liver (Bhattacharyya et al.).
The saga of the Richland americium case begins (Heid et al., PNL).
- 1980 New specific sequestering agents for actinides (Durbin, Berkeley).
NCRP report on management of persons accidentally contaminated
with radionuclides.
Twelve-year decorporation course reported in case of americium con-
tamination in Pittsburgh (Rosen, Wald, et al.).
- 1981 More on chelation research at Utah, including report of brain damage
in beagle fetus (Mays et al.).
Actinide-specific sequestering agents described in review (Raymond
and Smith, PNL).
- 1982 Summary of findings and effects of therapy in Richland americium case
published as special issue of *Health Physics*. Toxicity of Puchel reported
(Smith et al., U.K.).

Chapter 19

Therapeutic Procedures for Deposited Radionuclides

Overview

In the decade of the 1930s, concern for possible means of therapeutic removal of radium generated efforts that have gone on ever since, to either prevent deposition in tissues or remove deposits of radionuclides from the tissues of the body. The efforts never reached the stage of major programs such as those developed for pulmonary radiotoxicology or the understanding of the basic behavior and effects of deposited radionuclides. Nevertheless, some of the principal laboratories in the United States have had programs in almost continuous operation, and some individuals have devoted their scientific careers to the subject. Also, major installations with potential for serious contaminating incidents have been duty-bound to have facilities, personnel, and procedures at the ready in case of need. This chapter considers much of the research done to provide clinicians with useful methods for the therapy of contamination of humans with radionuclides.

Useful methods were indeed devised that clearly lengthened the life span and reduced suffering in cases, fortunately few, of significant contamination. The work also contributed in many ways to our understanding of how radionuclides are handled by higher organisms and to the possible roles of trace metals in normal physiological processes.

This chapter and the one to follow (on nuclear medicine) involve more overt interaction between laboratory research and clinical medicine than most of the earlier chapters in this book. They do not enter fully into recommendations for clinical practice, since this is in the domain of the clinical judgment of the cognizant medical team. They do, however, give easy access to most of the compendia containing specific recommendations for medical management.

Also in contrast to earlier chapters, in this chapter there is an almost equal mix of work done in the United States and in European laboratories. This is partly because the major developments were after World War II, except for some of the fundamental concepts of complexing, which developed in U.S.

laboratories near the end of the Manhattan District days. Active programs developed in the United Kingdom, West Germany, France, and the Soviet Union simultaneously with those in the United States. There was very active liaison among the groups, and each new idea got tested thoroughly on both sides of the Atlantic. For this reason, and because the U.S. effort was not the massive one characteristic of some other programs, work in several laboratories here and overseas is discussed simultaneously as appropriate to the subject matter at hand. We have had to eschew the careful chronology of contributions, laboratory by laboratory.

There is first a rapid review of the early attempts to mobilize radium by manipulation of calcium metabolism through diet and the use of drugs. The extensions of these attempts to radionuclides such as strontium that, like radium, behave as calcium does are woven into the picture essentially chronologically. There is also some exposition of the many efforts to influence metal metabolism by modification of normal physiological processes. This includes metal displacement and the use of colloid formers such as zirconium.

The bulk of our attention, however, is directed toward the development and role of various complexing agents and processes. It starts with the use of sodium citrate, the role of the war-time-developed British anti-lewisite (BAL), and then comes down hard on the chelators of the polyamino-polycarboxylic-acid type such as EDTA, DTPA, and their many derivatives. Included are some of the relatively recently developed agents such as the LICAMs, Puchel, etc.

In order to define the agents more or less uncluttered by details of the biomedical experimental work, there is a separate section (section III) devoted to a capsulized exposition of the rapid growth of complexing, especially by chelating agents. This is followed by details of the experimental work with animals, much of it in tabular form to allow the most extensive coverage in the least space (section IV). There is a separate section on treatment of inhaled radionuclides.

The section on experience in humans is divided into two parts: one concerned with experimental work at the tracer level; the other a review of some human contamination incidents in the United States that have come to therapy. While relatively few in number, these have been very thoroughly studied and documented. The findings are taken up in some detail herein.

An important feature in the use of these therapeutic modalities, particularly the chelating agents, has been the need to understand their intrinsic pharmacological behavior and their manifestations of toxicity. Some of this is inextricable from discussion of the experimental findings themselves. Yet, it seemed to require highlighting as a separate section (see Pharmacology and Toxicology of the Main-Line Chelators), particularly since the internal emitter establishment invested considerable effort in the pharmacology and toxicology of chelating agents.

There is no doubt that the preparations for therapy of deposited radionuclides have been worthwhile. Several lives have been saved—or at least materially extended. In this regard, the work merges with the much more common problem of therapy of the heavy metals such as lead, mercury, etc. Indeed, the internal emitter establishment benefited greatly by the development of agents by industry and in universities primarily for application to these more widespread problems and vice versa. In addition, the work has yielded insight into many basic aspects of how the body handles radioisotopes. These aspects could not be emphasized in the chapter to the extent they deserve, but they are hinted at wherever possible.

I. Introduction

In view of the high toxicity and long-term effects of many radionuclides when deposited in the body, it is not surprising that considerable effort has been expended to devise ways to prevent their uptake or deposition, to hasten their elimination, or to ameliorate their effects. This has applied especially to the long-lived elements that deposit in bone.

Prevention of uptake and hastening of elimination have received by far the most attention. Attempts to ameliorate the effects of deposited radionuclides by means other than prevention of uptake or deposition or by hastening of removal have little pertinence except for conventional medical and surgical procedures. It is true that toward the end of World War II and in the earlier postwar years, a large program was mounted, especially in laboratories associated with the Armed Forces, to attempt to reduce the effectiveness of absorbed doses from ionizing radiation. Almost all of the work utilized radiation sources external to the body and was applied primarily to single acute doses. A few substances were moderately effective. These have been catalogued as "radioprotective agents." However, they are generally effective only if present essentially at the time of irradiation. The protection afforded is very short-lived and would clearly be of even less use for internally deposited radionuclides since the radiation dose is much more prolonged than the action of the protective agent, and repeated doses of the protective agent are not practical.^(a)

Ideas pertinent to possible therapy of radium poisoning were investigated in the 1930s along with the crescendo of work on radium in animals and humans. We will recap the results briefly in the following section.

With the development of biomedical work on the fission products and the actinides during World War II, some attention was given to applying the procedures generated for radium to these new elements.

By far the largest effort went into the development of and experimental trials with various agents that could form complexes with the pertinent metals and thus, it was hoped, prevent their fixation in tissue or mobilize them for excretion if they had already been deposited. In this area, the workers with radioisotopes had much aid from the whole field of metal toxicology and the clinical experiences with common heavy metal poisons such as lead and mercury. Furthermore, the synthetic chemists had much more than the stimulus of scattered exposures to radionuclides to motivate them toward the development of new agents. The basic chemistry of these complexing agents received very concentrated attention and has been reviewed extensively.

The net result has been development of a few fairly standardized therapeutic procedures that are kept available in case of need. The agents themselves have sometimes turned out to be toxic in their own right, and frequently the desired therapeutic level cannot be attained or maintained because of the undesirable side effects of the therapeutic agent.

The laboratories and investigators concerned with the work on radioisotopes were largely those we have already identified with the internal emitter programs. Most of the major efforts in the United States were supported by the Atomic Energy Commission (AEC) and its successor agencies. Notable additions,

(a) The literature is so replete with reports of the work on radioprotective agents that no attempt will be made to review it here. Any good review of radiobiology will tell the story.

particularly on the clinical side, came from pharmacologists and physicians faced with major problems of heavy-metal poisoning. There have been major efforts also in other countries, especially England, France, Germany, and the Soviet Union.

Since the generation of therapeutic procedures for deposited radionuclides has received attention in relatively manageable proportions and has been concentrated in a relatively few institutions, reviews are both numerous and comprehensive.

II. Early Approaches

A. Radium

In the chapter on radium (primarily ^{226}Ra) we saw that ideas for "deleading" patients were proposed as early as 1926 by Dr. Joseph Aub and his many associates (e.g., Robley Evans, D. Hunter, R. McLean) at the Massachusetts General Hospital (MGH) and Massachusetts Institute of Technology (MIT). On the theory that radium would be at least as much like calcium as lead is, an approach to therapy was investigated through manipulation of calcium content of the diet and of calcium metabolism (e.g., by adding vitamin D, parathyroid hormone, etc.). A few patients and some animals with radium burdens were given this "deleading" type of treatment in 1937-1938. As indicated and referenced in chapter 1, it was possible by these procedures to increase radium elimination rates in the urine. However, the effect on total body burden of radium was disappointingly small. In the patients, the radium burden was usually of long standing, and the amounts accessible to removal without untoward perturbations of calcium metabolism were small.

Further work revealed that lead tagged with radiolead (^{210}Pb), and radium as well, deposit preferentially in trabecular bone, while the cortex remains initially relatively free of radioactivity. Gradually, the amount in cortex increases, presumably by migration from the trabeculae. Later work in Germany confirmed the presence of this pattern, this time using mesothorium. The deposit in cortex was in all cases much less mobile than that in trabecular bone. As the metal deposits in the apatite crystals, it becomes less and less available to mobilization. Additional work indicated that there are areas of greater and lesser mobility, even in cortical bone. At a meeting held at Argonne National Laboratory (ANL) in 1955, on therapy of radioelement poisoning, the field was reviewed in depth.

Dr. Aub gave an introductory address that elegantly reviewed the story of the classic contributions made to the field by these early studies on lead, radium, and calcium. A few of his remarks are reproduced below:

I have tried to give some idea of the work which a good many of us, mostly Robley Evans and myself, have done in the study of metal deposition in bone. After the metal gets deposited, then the problem is what to do about it, and that is the subject of this symposium.

There are several very discouraging things about therapy. If patients arrive for treatment early, the radioactive substances are in the trabeculae, an area from which they can be liberated. Many years later, as in the patients Dr. Evans and I have studied, radium is mostly in an area over which one has little control. Then it is mostly in the cortex; much less is in the trabeculae. The methods which we used then for decalcifying did increase the excretion rate of the radium about ten-fold. This is interesting but you are dealing with minutiae because the daily excretion rate is such a small fraction of a percent of the total metal stored.

One thing is very discouraging—the kidney is very ineffective in excreting radium. The amount of radium in the blood, at any given time, was the amount of radium which was excreted in the urine in 24 hours, so that the kidney did not excrete most of the radium which was presented to it. The kidney is, therefore, not efficient in excreting radium that is in low concentrations in the blood.

(Aub 1955)

Nevertheless, a fairly standard regimen was kept available (see section V).

B. Work in the Manhattan Engineer District

Obviously, the groups at Berkeley, in the Metallurgical Laboratory at Chicago, and at Rochester were aware of the earlier work with radium, lead, and other heavy metals. The pressure of finding out about the behavior of the new elements in the fission product and actinide series and the problems of uranium in large quantities left little time for exploration of means for therapeutic removal. Nevertheless, some work was done that is worthy of our review now.

The first mention of the possible importance of complexes to the behavior of fission products, plutonium, and uranium is found in a Metallurgical Laboratory memorandum from Jack Schubert to Waldo E. Cohn (Schubert 1945). As the title indicates, the thrust was as much toward methods for determining their composition and dissociation constants as toward their use in therapy.

At the date of Schubert's early work, quantitative data on the complex-forming properties of many substances depended on the classic frog heart method used in physiology and pharmacology. This was applied to the dissociation of calcium complexes since the beat rate of the frog's heart is a function of calcium ion concentration. The method had many limitations. Schubert proposed the use of ion-exchange methods, particularly for citrate complexes. He proposed an immediate program to investigate the citrate and tartrate complexes of strontium and of at least one rare earth.

Meanwhile, at Rochester, complexes of uranium with bicarbonate, protein, and citrate, and their biological importance, were being investigated and reported in the classified literature. This is reviewed briefly in chapter 2 and in the immediate postwar literature cited therein.

In 1946, the Berkeley group devoted a large part of one detailed report on strontium, yttrium, cesium, and plutonium to factors affecting absorption and retention (Copp, Greenberg, and Hamilton 1946). In the first chapter, they found, using adult female rats, that large cathartic doses of magnesium sulfate, sodium phosphate, sodium bicarbonate, etc., had little effect on absorption of radiostrontium (isotope not stated) from the gut. Only tricalcium-disodium phosphate, administered ten minutes after the radiostrontium, reduced absorption measurably. This agent is classed as an absorbent.

A high calcium diet also reduced gut absorption, even when given as discontinuous supplements. On a low calcium diet, absorption was elevated. By varying the periods on the diet, it was determined that the absorption depends more on the body's need for calcium than on the concentration in the gut at the time of administration of the radiostrontium. There was little effect of adding stable carrier strontium on the uptake of radiostrontium. Active growth had a significant effect as did also a prolonged period on a diet low in calcium. From these results, the authors suggested supplementing the normal human diet with dairy products or medicinal calcium to deter strontium uptake if such is anticipated. This was based on the premise that the human diet is usually low in calcium.

In the second chapter (same authors), they turn from oral to injected strontium. Parathyroid hormone, irradiated ergosterol, and a high citrate diet were used in addition to manipulations of calcium intake. Again, the only significant variables were age (rate of growth) and the state of calcium nutrition.

A third chapter (Copp, Chace, and Hamilton, same report) turns to the uptake of plutonium, yttrium, and cerium, in addition to strontium. There was again a marked effect of age and dietary calcium on strontium deposition in the skeleton. But there was no significant effect on plutonium, yttrium, or cerium isotopes.

The fourth chapter (Copp, Van Middlesworth, Cuthbertsen, Chace, and Hamilton) considers the effects of various treatments on *elimination* of deposited strontium, yttrium, cesium, and plutonium. They used parathyroid hormone, ammonium chloride, and sodium citrate; also a regimen consisting of a low-calcium diet, supplemented by ammonium chloride and parathyroid hormone, which is labeled as "the standard regimen commonly employed in treating chronic radium poisoning."

The procedures did increase the elimination of strontium somewhat, but not enough to materially reduce the body burden. They had no effect on the other elements.

A fifth chapter (Van Middlesworth, Copp, and Hamilton) describes uptake of radiostrontium, radioyttrium, and plutonium in healing fractures. Again, strontium was the most mobile, i.e., it reached the highest concentration in urine, although its peak occurred at about eight days, while those for plutonium and yttrium occurred somewhat earlier.

Severe phosphorus deficiency was the subject of the sixth chapter (Copp, Chace, and Hamilton). There was a fourfold reduction in retention of radiostrontium, but no significant effect on retention of plutonium, yttrium, or cerium. The phosphorus deficiency was severe and hardly a practical therapeutic modality.

Autoradiography of the bones, studied in the final chapter (Axelrod, Copp, and Hamilton) showed large areas of organic matrix free of bone salts. Plutonium, yttrium or cerium deposited in these. Strontium, by contrast, deposited only in the presence of bone salts. This work, along with earlier metabolic work, led to the conclusion that only strontium follows calcium metabolically. The other elements, basically of the rare-earth type, have metabolisms unrelated to calcium. This important conclusion has remained valid for decades and is still true, except that it is no longer accepted that plutonium et al. combine only with the osteoid matrix of bone.^(a) On this basis, therapy by manipulating calcium homeostasis would not be expected to do much except for strontium.

A final result of the autoradiographic study was the demonstration of overlayering of deposited radioisotopes by newly formed nonradioactive bone with consequent shielding of bone-marrow cells from alpha particles. This bears, of course, on the difficulty of therapeutic removal after a bone-seeking isotope has been in place for a considerable period.

The Chicago work on therapy of radionuclide deposition during the Manhattan Engineer District (MED) days examined the effects of sodium citrate

(a) Some of these same experiments and conclusions were published in the open literature in 1947, e.g., Copp, Axelrod, and Hamilton (1947). Others are quoted in chapter 7.

and of added hypertonic saline on excretion of plutonium. In the large report on clinical physiology of dogs injected with plutonium, which we examined in chapter 7 (Painter et al. 1946), the effect of these agents was described in one dog. The citrate was given to complex the plutonium following the ideas enunciated by Schubert, and the hypertonic saline was given to produce a diuresis. On the fifty-third day after receiving plutonium, the dog was fed 1.5-g sodium citrate capsules twice daily for ten days and then was given 0.7% sodium chloride twice daily by intravenous injection for seven days. The average urinary excretion rose from 0.005% of the injected dose per day to about 0.0065% of dose per day toward the end of the period of citrate treatment. It remained at about this level during the period when hypertonic saline was added. It quickly fell back to or even below the rate in the original control period on cessation of the treatment. A second period on hypertonic saline brought about a second rise, but only back to the 0.005%-per-day level.

This was hardly a dramatic result. Nevertheless, the authors felt that the approximately one-third increase in excretion rate was worthy of follow-up in cases where the plutonium had been present for a shorter period and was thus less "buried." Also, they speculated that citrate administrations twice daily would not maintain a high blood level of citrate for more than a small part of the day. They recommended more frequent citrate administrations.

These ideas were indeed followed out in post-MED work, but it is not clear whether or not these suggestions directly generated the later work. It is clear that the MED work added the idea of complexing of heavy metals to the systems based on diet and manipulation of calcium metabolism seen in the treatment of radium and lead poisoning.

C. Other Work During World War II

There was much activity in the Chemical Warfare Services of the United States and Britain that later bore fruit for the therapy of many types of poisonings. Both British and American laboratories were busy developing antidotes for the chemical warfare agents. Some of these agents contained metals like arsenic, and one of the antidotes was British anti-lewisite (BAL), which turned out to have dramatic effects against the arsenical, lewisite (Peters, Stocken, and Thompson 1945). We will discuss BAL and its uses more in sections III and IV.

In a more peaceful realm were the results of work by Seymour Kety on the use of citrate^(a) as a complexing agent for lead (Kety 1942). This appears to have been the *first suggestion*^(b) of the use of complexing as a *general* tool for decorporation of heavy metals in vivo.

There was, of course, much related activity in pharmacology and therapeutics during the war years. Radiotoxicology and heavy metal toxicology have shared the action for many decades. The early postwar reviews show the extent of this sharing.

(a) While the suggestion was unique and the arguments from stability constants persuading, citrate did not turn out to be a very effective agent in clinical cases of lead poisoning.

(b) Schubert's suggestion, made three years later and already cited, appears to be the first application of the idea to radioisotopes.

III. The Early Postwar Years—Complexing Agents Take Over

In the postwar years, the bulk of new contributions to the possible therapy of deposited radionuclides concern the development and use of complexing agents. It was a great expansion of the ideas generated during the war. Since the chemical character and biochemical actions of these agents must be understood before we can profitably discuss the experimental work, this section is devoted to a brief review of those subjects. Much more detail can be found in reviews to be cited in the section entitled "Review of Reviews."

A. Citrate and Other Normal Physiological Entities

Sodium citrate can form relatively strong complexes with metal ions, as was demonstrated during the years of World War II. At the second annual conference of the Utah Project (see chapter 8), Schubert (1954) expanded upon the ideas presented in the MED literature. He pointed to the rapid metabolism of citrate in the body as a probable reason for disappointing and spotty results. The complex with the metal does not exist for long unless new citrate is available. Destruction of the complex will release the metal again. In some cases, the effect may even be a negative one in that the complex may have carried the metal into tissue, e.g., bone. Therefore, methods such as continuous intravenous drip of citrate were suggested and even tried. The greater efficacy of other agents discouraged wide application of this clumsy method.

Meanwhile, a different approach was suggested, also by Schubert. Let the body make additional complexing agents *in vivo*! For example, relatively enormous amounts of citrate are produced daily in the course of normal tissue metabolism. It is usually broken down rapidly. However, sodium fluoroacetate, another product of research on chemical warfare agents that saw considerable postwar use as a pesticide, inhibits the reaction that breaks down citrate. Schubert describes tenfold to one hundredfold increases in citric acid content of soft tissues like spleen and kidney in animals given sublethal doses of fluoroacetate. He reports also reduction of lead burden when present in these animals by a factor of three in twenty-four hours. He apparently did not try the idea on radioisotope removal. Similar, but less marked effects can be obtained by blocking citrate formation by other means.

Schubert also had some ideas to help explain lack of efficiency *in vivo* when the *in-vitro* chemistry (e.g., stability constants) of the complexing agent and metal in question predicted success. These revolve around accessibility. In many cases, complexing agents do not enter the intracellular sites of deposition and thus remove only the amounts of radioisotope circulating in the blood, or in extracellular spaces. This was illustrated with citrate and lead. The disproportionately small removal of lead by citrate seems to occur when the lead is within the red blood cells. If the amounts of lead are sufficiently high so that the red cells are saturated and there are appreciable amounts in plasma, then the lead removed by citrate is relatively much greater. We will see presently that the question of accessibility is of great importance with all of the complexing agents.

Meanwhile, the ability of citrate to form soluble complexes with many heavy metals and radioisotopes thereof was utilized throughout the AEC, and in pharmacology and toxicology laboratories everywhere, to permit administration of the metals in a soluble form or to solubilize them for other purposes.

In many laboratories, detailed physicochemical work was done on the nature of the citrate complexes. At Rochester, for example, Feldman and Neuman (1953) worked with the uranyl-citrate system and did spectrophotometric studies.

Other naturally formed complexing agents have been tried. Among these are succinate, pyrophosphate, and bicarbonate. These are, in general, too labile to have much therapeutic potential. However, the work that developed our knowledge of them had great importance in suggesting how the metals are normally carried in vivo. It appears that calcium, barium, strontium, and probably radium are held in bone as complex ions. Any mobilization will depend upon both accessibility and the relation of the stability constants of the bone complex and the exogenous complex.

B. Metal Displacement—Colloid Formation—Zirconium

Work done at Chicago near the end of the war and reported in 1947 introduced a different idea from complex formation per se. This too was the brain child of Jack Schubert (Schubert 1947). He suggested, particularly for removal of plutonium, the administration of large amounts of metals with high valence, with metabolism similar to plutonium, and with very low toxicity. On the basis of mass action and ion exchange reactions, it was postulated that the administered metal would displace the plutonium (hence the term "metal displacement therapy").

In 1947, Schubert showed encouraging preliminary results in rats by administration of zirconium.^(a) Urinary excretion of plutonium was increased far above control levels and well above that resulting from doses of sodium citrate. The results are shown in table 19.1, taken from the Schubert paper.

A second injection of zirconium produced a second rise in plutonium excretion. There was no effect at any time on the quantity of plutonium excreted in the feces. Tissue analyses showed a significant reduction of the skeletal content of plutonium, as well as of that in liver. However, the amounts in muscle and kidneys were higher in the treated animals.

Schubert reported also on the effect of zirconium on plutonium excretion in a dog. He found the rise in excretion to be proportional to the amount of zirconium injected. It continued for about three weeks.

Rats treated five weeks after injection of plutonium showed a roughly tenfold increase in urinary excretion of plutonium after treatment with zirconium (compared to the fifteenfold increase when zirconium was given earlier after plutonium administration). In these animals, the liver content was reduced *but not that of bone*.

Zirconium treatment had only a negligible effect on excretion of strontium or its concentration in liver or bone. This led to the postulate that only those elements laid down in the uncalcified organic matrix of bone and in the endosteum and periosteum would be amenable to zirconium therapy.

In both the cited work and in a separate report (McClinton and Schubert 1948), the toxicity of zirconium, tested in rats, was found to be very low, and no long-term effects were noted. This finding, coupled with its apparent effectiveness, led to much experimental work with zirconium, including therapeutic

(a) He also tried cerium and lanthanum, all in their stable forms, but zirconium showed the most promise.

TABLE 19.1. Effect of Zirconium and Sodium Citrate Treatment on the Urinary Excretion of Plutonium in Rats*

(Data expressed as average per cent of injected dose of plutonium excreted each day)					
Days elapsed following Pu Injection	Pu Control	Treatment			
		Zirconium (100 mg on 2nd hr. and 3rd day after Pu injection)	Zirconium (50 mg. on 2nd and 24th hr. after Pu injection)	Sodium citrate (4 ml. of 10% sol. on 2nd hr. and 3rd day after Pu injection)	Sodium citrate (2 ml. of 10% sol. on 2nd and 24th hr. after Pu injection)
0-1	0.75	8.2	5.1	3.2	3.1
1-2	.051	.12	.66	.07	.68
2-3	.027	.032	.060	.037	.041
3-4	.041	.60	.078	.19	.041
4-5	.045	.022	.060	.016	.023
5-7	.022	.07	.058	.011	.018
7-10	.021	.064	.083	.020	.017
10-12	.024	.060	.059	.021	.010
12-14	.016	.064	.053	.026	.022
Total Pu excreted in urine for 14-day period. . .	1.1	9.6	6.5	3.7	4.0

* The rats (200-gram females) received 1.1 mg. of Pu/kg.

Source: Modified slightly and reset. from Schubert, 1947. Reprinted with permission of Science, Washington, D.C., copyright 1947.

trials in humans. We will review the latter in section V. Suffice it to say here that the promise was fulfilled in part, but toxicity problems were much greater than anticipated.

Later work showed considerable variation in the effectiveness of zirconium citrate for different radioelements. Relations to the formation of hydroxides with colloidal characteristics, especially the formation of small aggregates in the blood stream at physiological pH, were more consistent than the stability of the complexes. This led to consideration of agents like zirconium as "colloidal scavenging agents" rather than as simple metal displacers. The removal process thus might involve not only metal displacement but adsorption onto the colloidal aggregates. Under proper conditions, these aggregates were still small enough to pass through the kidney glomerulus into urine. A further reason for this postulate was that the final distribution was that of zirconium, not that of plutonium.

Whether ion exchange, coprecipitation, or colloid formation is the chief mechanism cannot be stated with confidence, but most workers at the time leaned toward the latter. Probably both occur, but in different proportions for different elements and conditions.

C. Chelation and Chelating Agents

The processes of complex formation and colloidal adsorption discussed in parts A and B are closely related to and lead into the processes and agents formally called "chelation" and "chelating agents." The term is derived from the Greek word *khēle* for claw. When two or more ligands in a molecule form coordinate bonds *simultaneously* with a metal atom, the chemical structure gives the appearance of a claw holding the metal atom. Such molecules are called chelating agents. The more "talons" there are in the claw the more stable the chelate, up to a point. The official terminology is to call compounds "unidentate," "bidentate," "polydentate," or "multidentate," etc., according to the number of ligands holding the metal. Classic groups for such binding are anions of oxo acids (e.g., $R-C=O$), neutral molecules which can donate a nitrogen atom (e.g., $R-NH_2$), etc. Thiol (i.e., $-SH$) groups also coordinate well with metal ions. However, the affinities are quite different among the ligands binding the metal.^(a)

The first chelation-type compound to receive general attention was the already-cited BAL, structurally a relatively simple compound.^(b) It is shown in figure 19.1A and as a metal complex in figure 19.1B. It forms coordination compounds with many metals.

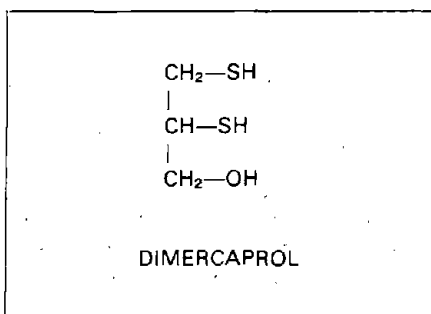


FIGURE 19.1A. Structure of British anti-lewisite.

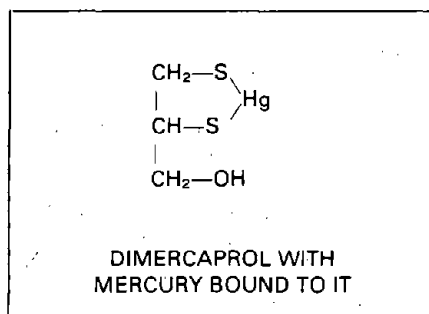


FIGURE 19.1B. British anti-lewisite as a metal complex.

As stated above, the work was begun by Rudolph Peters and colleagues (1945) in England. It has turned out that BAL is really effective for only a few metals but works very well when it does work.

Effects of BAL on radioisotope deposition and removal were studied primarily at ANL and the University of Rochester. We will examine details in the next section. While there were a few instances of notable success with BAL, the cadre

(a) The difference between ordinary electrovalent binding and covalent binding, the process involved with these compounds, is that the organic portion of the molecule contributes both valences. This contrasts to ordinary binding where an anion contributes an electron to a deficient cation to form a stable union. In complexing or coordinate binding, the metal frequently loses its original properties as an ion. (Actually this happens to some extent with citrate binding, but the characteristic "claw" structure is not so prominent.) The result of this loss of original properties as a metal ion is sometimes advantageous; sometimes it poses problems.

(b) The chemical name is 2,3 dimercaptopropanol, sometimes shortened to dimercaprol.

was small, and soon other substances were investigated as chelating agents. Thus, the polyamino-polycarboxylic acid chelating agents came on the scene. A tabulation of the structure, abbreviations, and full chemical names for some of these is given in table 19.2.

TABLE 19.2. Polyaminocarboxylic Acids Employed in Therapeutic Removal of Heavy Metals

Abbreviation	Name	Structural Formula
EDTA	Ethylenediaminetetraacetic acid	$\begin{array}{c} \text{HOOCCH}_2 \quad \text{CH}_2\text{COOH} \\ \diagdown \quad \diagup \\ \text{NCH}_2\text{CH}_2\text{N} \\ \diagup \quad \diagdown \\ \text{HOOCCH}_2 \quad \text{CH}_2\text{COOH} \end{array}$
DTPA	Diethylenetriaminepentaacetic acid	$\begin{array}{c} \text{HOOCCH}_2 \quad \text{CH}_2\text{COOH} \\ \diagdown \quad \diagup \\ \text{N-CH}_2\text{-CH}_2\text{-N-CH}_2\text{-CH}_2\text{-N} \\ \diagup \quad \diagdown \quad \diagup \quad \diagdown \\ \text{HOOCCH}_2 \quad \text{CH}_2\text{COOH} \quad \text{CH}_2\text{COOH} \end{array}$
TTHA	Triethylenetetraminehexaacetic acid	$\begin{array}{c} \text{HOOCCH}_2 \quad \text{CH}_2\text{COOH} \\ \diagdown \quad \diagup \\ \text{NCH}_2\text{CH}_2\text{-N-CH}_2\text{CH}_2\text{-N-CH}_2\text{CH}_2\text{-N} \\ \diagup \quad \diagdown \quad \diagup \quad \diagdown \quad \diagup \quad \diagdown \\ \text{HOOCCH}_2 \quad \text{CH}_2\text{COOH} \quad \text{CH}_2\text{COOH} \quad \text{CH}_2\text{COOH} \end{array}$
BAETA	2,2'-bis-[di(carboxymethyl)amino]diethyl ether	$\begin{array}{c} \text{HOOCCH}_2 \quad \text{CH}_2\text{COOH} \\ \diagdown \quad \diagup \\ \text{N-CH}_2\text{CH}_2\text{-O-CH}_2\text{CH}_2\text{-N} \\ \diagup \quad \diagdown \\ \text{HOOCCH}_2 \quad \text{CH}_2\text{COOH} \end{array}$

Source: Modified from Thompson 1967. Reprinted with permission of American Nuclear Society, LaGrange Park, Illinois, copyright 1967.

Many of these compounds were synthesized for other purposes, primarily for increasing solubility of other substances. Indeed, the first member of the group, EDTA, is the old detergent, "Versine" or "Versene," the terminology depending upon geography.

A flurry of activity took place in the early 1950s around EDTA. In fact, it appears that EDTA was first tested at Berkeley for the removal of plutonium from animals (Foreman 1950), and the work toward complexing stable heavy metals followed. Berkeley, Chicago, Hanford, Los Alamos, and the Naval Radiological Defense Laboratory were particularly involved. In Europe, there was much activity: e.g., in the United Kingdom, Dame Janet Vaughan at Oxford University and Professor David Taylor at the Royal Cancer Hospital; in West Germany, in the laboratory of Professor Alexander Catsch at the Karlsruhe Institute; in France at J. C. Lafuma's laboratory at Fontenay-aux-Roses, and also at laboratories in the Soviet Union.

This work involved both experiments with animals and therapeutic applications in man as well as the development of agents such as DTPA, etc., cited in table 19.2.

Since all of these compounds form stable complexes with calcium, great care is needed to prevent undue removal of body calcium and the serious consequences thereof. One of the chief problems has been striking a suitable balance between complexing of the unwanted metal and withdrawal of undesirable amounts of calcium from the blood and body stores.^(a) To guard against this,

(a) Removal of other essential metals is also a potential problem but of less significance (see the next section).

calcium is now always given along with the chelating agents. In figure 19.2A, the formula for sodium EDTA is repeated, along with a postulated reaction in which calcium enters the chelate and sodium is released. The binding of other metals is presumed to occur in the same way as shown for calcium. Another possible structure of the calcium complex is shown in figure 19.2B. Both formulae are from a paper given by Harry Foreman at the Second Annual Utah Conference (see chapter 8) where the possibilities for the polyamino-polycarboxylic acids were first expanded upon (Foreman 1954, 1955).

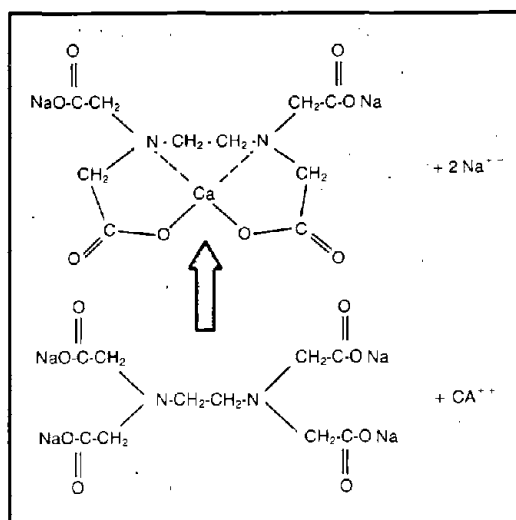
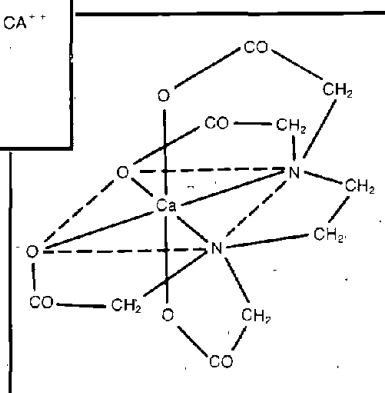


FIGURE 19.2A. (Left) Possible structural formula of EDTA and its complex with calcium. (Redrawn from Foreman 1954. Reprinted with permission of the University of Utah Press, Salt Lake City, Utah, copyright 1954.)

FIGURE 19.2B. (Right) Alternative structure for the calcium chelate with EDTA. (Redrawn from Foreman 1954. Reprinted with permission of the University of Utah Press, Salt Lake City, Utah, copyright 1954.)



Obviously, a large amount of good chemistry was needed to measure dissociation constants (or stability constants) of the many chelating agents with the many metals of importance, both endogenous and exogenous. The in-vitro work was done well, and predictions of general validity could be made regarding the potential efficacy of a given agent toward a given metal. However, as the experimental work progressed, there were many surprises, and many predictions were only partially fulfilled. In the stable metal area, there were so many surprises that the workers began to feel that our knowledge of how heavy metals act was really very deficient. In the radioisotope area, there were surprises too, but since the effects were from a common cause, ionizing radiation, usually uncomplicated by the biochemical effects of the metal ion itself, the dilemmas were actually less profound.

Before we proceed to examine the experimental work, another set of chelating agents needs introduction. These are agents that have special affinity for

iron. There is a family of such agents. One of them is desferrioxamine (DFOA), which is produced microbiologically and has enjoyed some success in treatment of iron poisoning and iron storage diseases. Structurally it looks grossly like the members of the EDTA group, but the complex with iron is entirely through oxygen linkages (Keberle 1964, cited by Vaughan 1973). The structure is shown in figure 19.3A and B. Since plutonium chemistry and iron chemistry have many parallels, this agent and some other iron chelators have been tried experimentally to remove plutonium and other actinides (Taylor 1967; Durbin et al. 1980). This agent seems to be ineffective for actinides other than plutonium.

FIGURE 19.3A. Iron chelator structure—desferrioxamine chemistry. (Redrawn from Keberle 1964 via Vaughan 1973. Reprinted with permission of Springer-Verlag, New York, copyright 1964.)

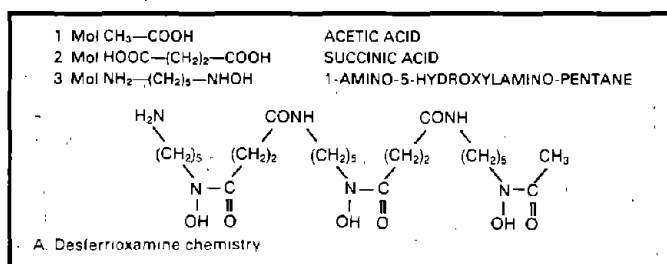
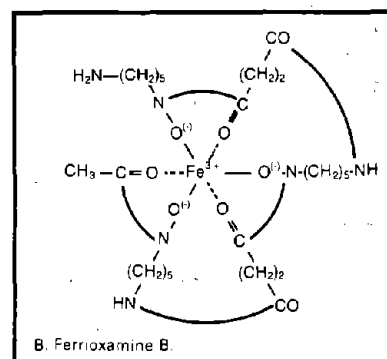


FIGURE 19.3B. Iron chelator structure—ferrioxamine B. (Redrawn from Keberle 1964 via Vaughan 1973. Reprinted with permission of Springer-Verlag, New York, copyright 1964.)



A host of other agents have been tried for therapy of deposited radionuclides. In fact, it sometimes appears that there are few things that have *not* been tried for therapeutic removal of metals and of their radioisotopes. However, these do not routinely fall into the category of complexing agents per se and will be discussed when relevant to the development of the experimental work.

D. Review of Reviews^(a)

Because of the close relationship between all of chelation chemistry, heavy metal toxicology, and many important clinical problems, it may be useful to list here a few of the most pertinent reviews that will give background for our discussion of the experiments in the radioisotope field. Some are mostly chemical in orientation, others provide biomedical findings parallel to those we have introduced and will discuss further in sections IV and V. A short annotation accompanies some of the reviews.

(a) The venerable Chauncy Leake, one of the founders of the *Annual Review of Pharmacology*, capped off each volume with a "Review of the Reviews" in that volume. I have borrowed his title for this section.

The reviews^(a) are:

1. Reviews by Schubert and Foreman in *Second Annual Conference on Plutonium, Radium and Mesothorium*. University of Utah Radiobiology Laboratory. C. N. Stover, ed., 1954.
2. "Chelating Agents." by Harry Foreman. A reprint of the chapter from the Utah symposium; in *Industrial Medicine and Surgery* 24, (7), 1955.
3. *Therapy of Radioelement Poisoning*. AEC Report ANL-5584, 1956. A symposium was held at ANL in 1955 and edited by Marcia White Rosenthal. Contains early clinical as well as experimental work on a variety of agents. The appendices contain summary tables of work to date of writing.
4. *Metal Binding in Medicine*. Book edited by M. J. Seven and L. A. Johnson (1960). A very broad spectrum of chapters on all aspects of the subject from basic chemistry and pharmacology to specific disease entities. From a symposium held at Hahneman Medical College, Philadelphia.
5. *Diagnosis and Treatment of Radioactive Poisoning*. International Atomic Energy Agency, Vienna, 1962. Proceedings of a meeting sponsored jointly by WHO and IAEA. Contains sections on radium, strontium, other fission products, plutonium and other transuranium elements, and treatment plans. International flavor.
6. "Therapeutic Removal of Transuranic Elements." Section in Hanford symposium, *Biology of the Transuranic Elements*, 1962. *Health Physics*, 8(6). Includes paper by Catsch on principles and trends.
7. "Toxicology: Inorganic." Chapter by Harry Foreman in *Annual Review of Pharmacology*, Vol. 2, 1962. Concerns stable metal complexing primarily.
8. "In Vivo Factors Influencing the Efficacy of Chelating Compounds as Therapeutic Agents for Metal Toxicity." H. Foreman. In *Drugs and Enzymes*. Proceedings of an international meeting in Prague, August 1963. Pergamon Press. A broad review of chemical principles and specific studies.
9. *Iron Metabolism*. An international symposium sponsored by CIBA, at Aix-en-Provence, France, July 1963. Springer-Verlag, Berlin. Much overlap between iron and substances of interest in this chapter.
10. "Prophylactic and Therapeutic Measures." Section in Hanford symposium, the *Biology of Radioiodine*, *Health Physics*, 9(12), 1963.
11. "Treatment for Removal of Inhaled Radioactive Particles." Section in Hanford symposium, *Inhaled Radioactive Particles and Gases*. *Health Physics*, 10(12), 1964.
12. *Radionuclide Contamination and Removal*. W. J. Bair and V. H. Smith (1969). In: *Progress in Nuclear Energy, Series XII*.
13. *Metal-DTPA Chelates in Biological Systems: A Bibliography*. V. H. Smith. Pacific Northwest Laboratory Report, BNWL-1657, 1972. In addition to the listings, which are arranged by element, the animal species under investigation are also listed.
14. "Acceleration of the Excretion of Actinide Elements." J. Vaughan et al. In chapter entitled "Metabolism and Biological Effects of Plutonium as a Bone Seeker." In: *Uranium, Plutonium, Transplutonic Elements, Handbook of Experimental Pharmacology, New Series*, Vol. 36, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh. Springer-Verlag, 1973, p. 471 et seq. Extensive summarization of EDTA, DTPA, BAETA, and others.
15. "Therapeutic Removal of Plutonium from the Lung." In chapter entitled "Plutonium in Soft Tissues with Emphasis on the Respiratory Tract." W. J. Bair et al. In: *Uranium, Plutonium, Transplutonic Elements, Handbook of Experimental Pharmacology, New Series*, Vol. 36, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh. Springer-Verlag, 1973, p. 562 et seq. Contains tabulation of tests for removal of inhaled plutonium dioxide.

(a) Several of these reviews are utilized in more depth in the text. If so, they are cited fully in the references. Otherwise, the above citations are sufficient to lead the reader to the volumes.

16. "Acceleration of the Excretion of Actinide Elements." In chapter entitled "Metabolism and Biological Effects of the Transplutonium Elements." P. W. Durbin. In: *Uranium, Plutonium, Transplutonic Elements, Handbook of Experimental Pharmacology, New Series, Vol. 36*, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh. Springer-Verlag, 1973, p. 853 et seq. Contains tabulation of DTPA work.
17. *Diagnosis and Treatment of Incorporated Radionuclides*. Proceedings of a WHO-IAEA seminar, held in Vienna in 1975. Contains several important review papers and international coverage. More on assessment than many earlier reviews.
18. *Chelation Therapy in Chronic Iron Overload*. A CIBA symposium. New York City, May 1977. Eds. C. Zaino and R. H. Roberts. Strathier Intercontinental Medical Book Corporation, New York. A series of very specialized papers.
19. *Treatment of Incorporated Transuranium Elements*. A report by V. Volf sponsored by WHO and IAEA and published as IAEA Technical Report Series No. 184, 1978. A comprehensive review.
20. *Selective Toxicity. The Physico-Chemical Basis of Therapy*. Adrian Albert. Sixth Edition. Chapman and Hall, London. A broad review of all aspects of selectivity, with a special section on metal-binding substances and the covalent bond.
21. "Actinide-Specific Sequestering Agents and Decontamination Applications." K. N. Raymond and W. L. Smith. In: *Structure and Bonding*, Vol. 43. Eds. Goodenough et al., Springer-Verlag, Berlin, 1981. Very detailed chemistry.
22. "Specific Sequestering Agents for the Actinides 4. Removal of ^{238}Pu (IV) from Mice by Sulfonated Tetrameric Catecharyl Amides." P. W. Durbin et al., *Radiat. Res.*, 81, pp. 170-187, 1980. While specific experiments are reported, much of the paper concerns general chemical problems.
23. *Management of Persons Accidentally Contaminated with Radionuclides*. G. L. Voelz, H. D. Bruner, T. A. Lincoln, V. H. Smith, H. Spencer, and N. Wald. NCRP Report 65, 1980.
24. "Therapy for Incorporated Radionuclides: Scope and Need." V. H. Smith. In: *Actinides in Man and Animals*, ed. M. E. Wrenn, 1981. RD Press, Salt Lake City.
25. "Status of Chelation Research: A Review." C. W. Mays, G. N. Taylor, R. D. Lloyd, and M. E. Wrenn. In: *Actinides in Man and Animals*, ed. M. E. Wrenn, 1981. RD Press, Salt Lake City.
26. "Recent Research on Decorporation Therapy at National Radiological Protection Board." G. N. Stradling and R. A. Bulman. In: *Actinides in Man and Animals*, ed. M. E. Wrenn, 1981. RD Press, Salt Lake City.
27. "Chelation Research at the Institute of Environmental Medicine, New York University Medical Center." Norman Cohen. In: *Actinides in Man and Animals*, ed. M. E. Wrenn, 1981. RD Press, Salt Lake City.
28. "Comments on Chelation Therapy." M. E. Wrenn. In: *Actinides in Man and Animals*, ed. M. E. Wrenn, 1981. RD Press, Salt Lake City.
29. "Removal of Inhaled Plutonium and Americium from Dogs Using Lung Gavage and DTPA." B. A. Muggenburg, J. A. Mewhinney, R. A. Guilmette, and R. O. McClellan. In: *Actinides in Man and Animals*, ed. M. E. Wrenn, 1981. RD Press, Salt Lake City.

IV. Experimental Work with Animals in the Postwar Era

In this section, we will give considerable detail and some summary tables that expand upon the preview given in section III. The approach is largely chronological for the major groupings. Emphasis is placed upon the principal developments during the years of AEC sponsorship, with less attempt to discuss recent work, which is readily available to the reader.

A. Zirconium

We have already cited the ideas put forward by Jack Schubert during and just after the Manhattan Engineer District days. We have shown a table from his 1947

publication comparing zirconium and sodium citrate effects on excretion of plutonium in rats (table 19.1).

More detailed reports from the ANL group compared effects of zirconium administration on plutonium and yttrium metabolism in both dog and rat (Schubert 1949; Schubert and White 1950b). Since plutonium is an alpha emitter and yttrium a beta emitter, the two radionuclides could be given and measured simultaneously in the same animal, thus eliminating some of the problems of animal-to-animal variation in excretion rates. They compared the effectiveness of "early" sodium citrate, "early" zirconium citrate, and "late" zirconium citrate. (a) The effects on both excretion and tissue contents are illustrated in figure 19.4A for plutonium and figure 19.4B for yttrium.

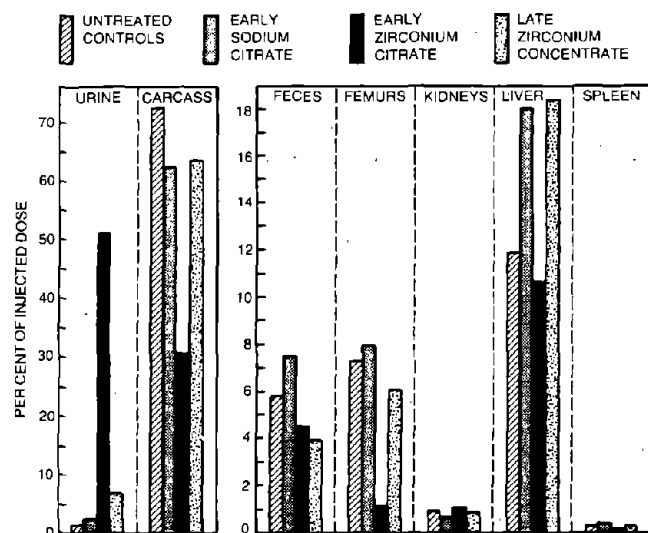


FIGURE 19.4A. Distribution and excretion of plutonium (Pu^{239}) in untreated and treated rats. Effect of zirconium and sodium citrate treatment on the distribution and excretion of $\text{Pu}(\text{IV})$ in rats six days after the intraperitoneal administration of the radioelement. (Redrawn from Schubert and White 1950b. Reprinted with permission of the American Society of Biological Chemists, copyright 1950.)

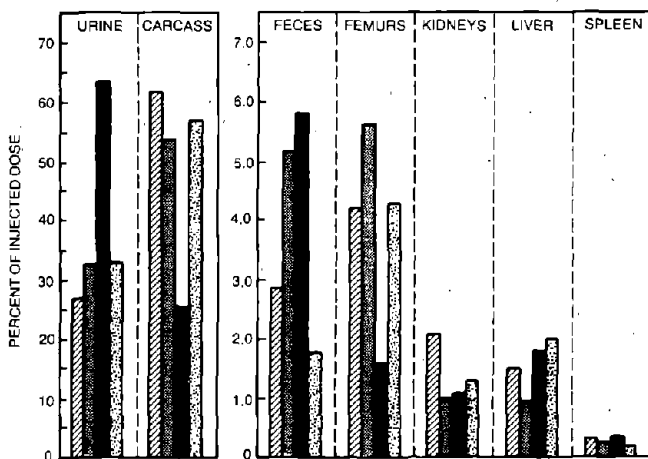


FIGURE 19.4B. Distribution and excretion of yttrium (Y^{91}). Effect of zirconium and sodium citrate treatment on the distribution and excretion of Y^{91} in rats six days after the intraperitoneal administration of the radioelement. (Redrawn from Schubert and White 1950b. Reprinted with permission of the American Society of Biological Chemists, copyright 1950.)

(a) "Early" = thirty minutes after intraperitoneal injection of the radionuclide. "Late" = seventy-two hours after intraperitoneal injection of the radionuclide.

Obviously, early treatment with zirconium citrate placed more plutonium in urine and resulted in less retention in carcass, femur, and liver, while late treatment had much less effect. There was little increase in fecal excretion of plutonium, but the zirconium, if given early, increased fecal excretion of yttrium. Note, too, how much more plutonium than yttrium was in liver.

The effects of zirconium in a single dog were as described earlier, with a surprisingly large effect on plutonium, which had been in residence for five months or even 2.5 yr. (Yttrium was not tried in the dog.)

Further work went from a single dose of zirconium to multiple doses and different dose levels (Schubert and White 1950b). Plutonium and yttrium excretion was proportional to the size of the dose, but reduction in skeletal content was essentially independent of the dosage given, above about 10 mg/kg body weight, and of the number of doses. Liver retention of plutonium increased with zirconium dose up to about 25 mg/kg body weight and then decreased. Liver retention of yttrium was little affected by changes in zirconium dosage.

These results, while not overwhelming, encouraged further trials, especially since the skeletal content of the animals was materially reduced, a sharp contrast to the attempts to reduce radium burdens by the techniques then at hand.^(a)

In a separate study, Schubert and White (1950a) showed that zirconium was effective in removing beryllium from rats. They used the radioisotope of beryllium, ^7Be .

By the time of the 1955 meeting at ANL on therapy of radioelement poisoning, the Marcia White listed above as a collaborator with Schubert had become Marcia White Rosenthal. Not only that, she edited the proceedings. At that meeting, she gave further information on the use of zirconium (Rosenthal 1956). She emphasized the growing evidence that the mechanism of zirconium action is a carrier effect on the *circulating* radioelement. Only the portion of the radionuclide in circulating blood (and perhaps extracellular fluid) becomes attached to the colloidal aggregates. The subsequent behavior of the element, i.e., disappearance from blood, deposition in tissues, and excretion is that of the zirconium-radioelement aggregate. She again stressed the effect of dosage size and regimen using many of the same animal data cited earlier. Zirconium treatment was ineffective for metals like strontium and magnesium.

Probably the most important lesson learned from this work, besides the presence of some effect, was the importance of prompt treatment.

Very soon, the Hanford group picked up the trail of zirconium therapy. They had much reason for interest since they were handling more plutonium than anyone else. In early annual reports of the Biology Division, Joffe and Temple (1953) and Wager and Temple (1954) (summarized by Thompson [1956]) found that zirconium produced even larger decreases in liver and skeletal contents of plutonium in the dog than in the rat. Also, it turned out that the dose needed to prevent bone deposition was lower than that needed to produce maximal excretion in the rat. Unfortunately, these doses seemed to *promote* accumulation in soft tissues. This work is summarized and referenced by Thompson (1967).^(b)

(a) This author can find no record of zirconium being tested for the removal of radium. Probably the fact that it did not mobilize calcium was taken as an indication it would not work for radium.

(b) A paper from Hanford by Katz, Weeks, and Oakley (1954), which compares various agents, also includes work on zirconium.

The Berkeley group apparently did not try zirconium for plutonium. However, they did test it for ^{90}Y (Copp and Kavin 1956). There was a marked increase in the excretion of ^{90}Y (16.4% to 91.2%) and very little bone retention in the treated animals.

Zirconium was also tested at the Naval Radiological Defense Laboratory (NRDL). Animal work was done by Stanton Cohn and utilized the variety of fission product surrogates, simulants, and prepared mixtures described in chapter 9. Cohn's work (1956) utilized zirconium largely in combination with chelating agents and will be described in section IV C.

By 1955, at least fourteen experiments with zirconium in animals (some of them parts of a several-experiment report) had been completed. These can be reviewed in the very useful table given in Appendix I of the ANL symposium volume (Report ANL-5584, 1956, see item 3 in "Review of Reviews").

Because of the urgency to have some form of treatment available for in-plant exposures, the Hanford group and others arranged to have zirconium available in proper form in their treatment rooms. It was used clinically both in the United States and the United Kingdom for a few cases, as described in section V.

To indicate that such readiness for therapy was more than academic, table 19.3 shows the existence of at least forty-five cases of low-level plutonium deposition at Hanford over a ten-year period up to about 1955. It is not stated which, if any, of these received therapy. Even if none did, the very presence of that number of cases bespeaks the need for having potential therapy available.

TABLE 19.3. Hanford Plutonium Deposition Cases in 10 Years

Per cent of MPL	First Detection By Routine Samples	First Detection After Known Incident	Route of Intake on Known Incident Cases				
			Inhala- tion	Inges- tion	Absorp- tion	Injec- tion	Un- known
<0.5	4	29	25	1	3		
0.5 to 1.0	7	4	2		2		
1.0 to 10	13	13	8		4	1	
10 to 20	4	6	5			1	
20 to 50	0	1	1				
50 to 100	2	0					
>100	0	0					
Partial Inter- pretation	15	2					2
	45	55	41	1	9	2	2

Source: Reset from Thompson 1956, originally from H. M. Parker's paper at first Atoms for Peace Conference.

As we will see, the clinical experience with zirconium exposed problems not seen in the animal work and caused a considerable decrease in the urge to do further experimental work. Indeed, what we have reviewed, except for some

work aimed at interpretations of mechanism and combination therapy, about completes the story of zirconium therapy in animals in the United States.^(a)

B. British Anti-Lewisite

Experimental work in animals for removal of radionuclides with BAL (structure on page 1595) was definitive but not extensive. This stands in considerable contrast to the large amount of work done toward removal of stable heavy metals with BAL (cf. Doull, Klaussen, and Amdur 1980).

One of the earliest experiments aimed toward radionuclide removal concerned Thorotrast in rabbits. Björn E. W. Nordenström-Blomqvist, working at "a hospital in Stockholm," reported (1950) on the excretion of ThX (^{224}Ra) and MsTh (^{228}Ra) in urine. There was no effect of BAL on the excretion of these thorium decay products, nor was there any measurable excretion at all of thorium itself with or without BAL.

More experimental work was done on removal of polonium with BAL than on any other radionuclide. It was carried out at the University of Rochester, primarily by John B. Hursh. Like all of Hursh's work, which we have already seen in the chapters on radium (chapter 1), uranium (chapter 2), and polonium and thorium (chapter 4), it is carefully and authoritatively done, covers nearly all aspects of the problem, and forms a very neat package. The first work (Hursh 1949, 1951) concerned in part^(b) excretion and tissue distribution of ^{210}Po given as a single intravenous injection. Polonium excretion over a ten-day period was doubled on a dosage regimen where BAL was given at one hour after the polonium followed by three doses per day at intervals of no less than three hours for a total treatment period of three days. The average ten-day urinary excretion rate was 1.39% of the dose with BAL compared to 0.64% of the dose without BAL. Fecal excretion averaged 52.1% of the dose in ten days with BAL compared to 25.1% of the dose over a ten-day period without BAL. Thus, the most significant effect was via the increase in excretion in feces. Both rates reached their maxima at about five days, i.e., two days after cessation of treatment.

The changes in excretion were sufficient to reduce the total body burden, and, importantly, the BAL treatment caused a redistribution of polonium away from radiosensitive tissues like bone marrow, spleen, and testis and into a radio-resistant tissue, muscle. These results are shown in figure 19.5.^(c)

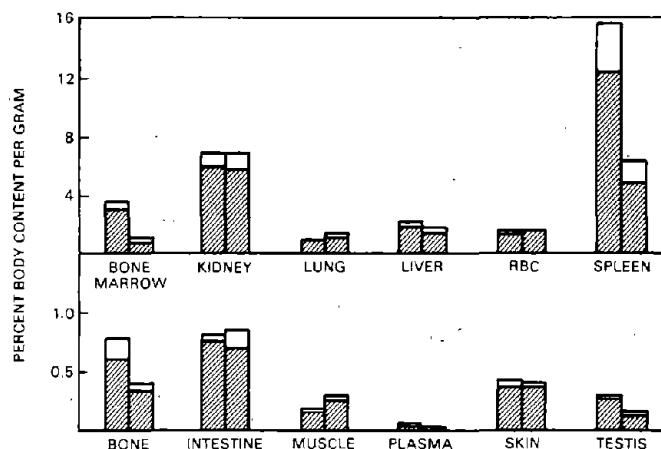
Investigation of the earlier changes in tissue distribution indicated that some of the changes shown in figure 19.5 at ten days after administration of the polonium also occurred at three hours. However, kidney and intestinal contents were *increased* in the BAL-treated animals at three hours, whereas at ten days, these organs were no different from those of controls. One of the most striking changes, which was measured by frequent sampling out to ten days, occurred in

(a) Interest continued in European laboratories somewhat longer. At the International Radiation Protection Association (IRPA) Congress on internal contamination published in 1973, some workers from Czechoslovakia discussed use of zirconium for removal of cerium and strontium (Severa 1973). There was a significant mobilization of cerium from both liver and bone, very little effect on strontium.

(b) The original University of Rochester Project Report (Hursh 1949) contains other information also, which will be considered presently.

(c) Polonium is not a bone seeker. The amounts shown in bone in figure 19.5 reflect primarily polonium in organic combination and in marrow.

FIGURE 19.5. The average tissue percent body content of polonium as determined in animals sacrificed at ten days is plotted in the first column for control rats and in the second column for five BAL-treated rats. The height of the shaded rectangle is equal to the average value; the superimposed open rectangle denotes the associated standard error. (Redrawn from Hursh 1951. Reprinted with permission of the Williams & Wilkins Co., Baltimore, Maryland, copyright 1951.)



the blood. The amount of polonium in blood was markedly diminished in the BAL-treated animals out to at least four, perhaps six days. We will return to this point.

To see if the changes in tissue distribution really make a difference in the effects of the polonium, Hursh (1952) carried out a survival experiment. Using the extensive background in acute toxicity work with polonium at Rochester, Hursh chose doses in the midlethal range and compared survival times as well as hematologic changes with and without BAL treatment. The treatment regimen was the same as in the earlier experiment (Hursh 1951). There was no doubt that the survival time was significantly increased (median, twenty-two to twenty-five days in untreated animals, eighty-nine days in the treated). This increase was larger than could be accounted for by the increased excretion alone (based on the established survival curves developed by Fink et al. and presented in chapter 4). The mobilization of polonium from radiation-sensitive tissue to a radioresistant tissue, such as muscle, must have played an important part. The blood red cell, white cell, and platelet counts were consistent also with the idea that spleen and bone marrow received a reduced radiation dose in the BAL-treated animals.

Hursh did not leave the work at the observational stage only however, a defect in some of the other research we have considered in this book. He went on to investigate possible mechanisms. In the 1951 study, he determined the polonium content of red cells, plasma, and plasma dialyzed for four hours against buffered saline. Despite the significant decrease of polonium content of both red cells and plasma, mentioned above, about seven times as much appeared in the plasma dialysate in BAL-treated rats. It could therefore be postulated that the BAL forms a soluble complex with polonium through the dithiol group in competition with its normal binding to tissues. This complex is presumed to filter readily through the kidney glomerulus and into the urine. Further, with the well-known tendency of polonium to form hydroxide colloids at neutral pH, which colloids are taken up by the reticuloendothelial system, it

can be further postulated that the diversion from spleen and bone marrow represents a reduction in these colloid moieties in favor of a soluble complex.^(a)

Hursh points out the contrast between the behavior of polonium bound to BAL and that of arsenic bound to BAL. In the latter case, there is a sharp rise in blood concentration of arsenic coupled with increased urinary excretion. The mobilization process is thus the converse of that seen with polonium. We will see that this is a common mechanism with the polyamino-polycarboxylic chelators of the EDTA type. Unfortunately, not all of the experimental work with EDTA-type chelators has gone as far as Hursh's work toward pinpointing a double mechanism: increased excretion and tissue redistribution.

Stannard and Haydon (1956) tested the effect of BAL on distribution and excretion of polonium given orally rather than intravenously. This was done since polonium exposures can be oral and a fraction of any inhalation exposure includes material cleared from the lung to the gut (see chapter 9). Effects on urinary excretion rates were not significant over a nine-day period. Fecal excretion was decreased (significant at $p \leq 0.05$), although not markedly (87.3% in nine days versus 93.4% in control animals). Tissue distribution of the absorbed polonium was *not* altered as it was after intravenously administered polonium. In fact, the most striking effect of BAL was an *increase in gastrointestinal absorption of polonium and consequent increased body retention of orally administered polonium*. Obviously, whatever solubilization occurred promoted absorption. The tissue distributions indicate the presence of a different form of polonium in blood after absorption from the gut, one not amenable to complexing with BAL, perhaps because it was already in a more soluble form (see chapter 4).

Further indications of such differences in state of polonium in the blood are found in earlier findings by Hursh (1949). For example, BAL was much less effective against polonium given subcutaneously than when given intravenously.^(b)

This work on polonium indicated possible therapeutic potential. However, the effect of route of administration and the fact that effects on inhaled polonium never got studied left some reasons for conservatism in possible application to humans.

The rest of the experimental work with BAL and radionuclides is largely negative. Kavin and Copp (1953) at Berkeley tried it for plutonium in rats. Kisielski, Norris, and Woodruff (1951) at Argonne tried it for ^{32}P and ^{90}Sr . Neuman and Allen (1949) tried it at Rochester for removal of uranium. All showed either no effect at all or short-lived unimpressive effects.

This series of negative results should not be construed as eliminating BAL as a potential therapeutic agent for radionuclides. Even though some of the more important potential contaminants were not affected, many elements remain untested even now. Also the radioisotopes of those elements whose mobilization in stable form has already been demonstrated would presumably

(a) Actually, more than one state of polonium exists in normal blood, an early diffusible state and poorly diffusible aggregates or combinations with protein or other carriers. The tight binding, once established, is difficult to reverse. Fortunately, it appears that the loosely bound fraction persists for appreciable periods and thus gives the BAL a chance to act.

(b) Some other sulfhydryl compounds, viz., "NDR-399" and "NDR-317" (see Hursh 1949) were more effective than BAL under these conditions.

behave similarly. The primary reason for termination of the work with BAL was the development of the more versatile chelators and a factor of unpleasantness in the use of BAL, viz., the typical unpleasant odor characteristic of many thiol compounds.^(a)

C. The Main-Line Chelators

By "main-line chelators" we mean those substances that have been used most frequently and have had, in general, the greatest success, particularly against contamination by the transuranics and the bone seekers in the fission product chain. These are EDTA, DTPA, TTHA, BAETA (table 19.2), and the additional polyamino-polycarboxylic acids and other substances.^(b)

1. The Actinide (Transuranic) Elements

a. Mobilization

We will begin with a tabular review of animal work directed toward removal or "decorporation"^(c) of plutonium and several other transuranium elements after intravenous administration of the radionuclide to rats. This review is shown as table 19.4, modified from the book by Volf (1978).

(a) *Note added in proof:* It turns out that neither the polonium nor the disulfhydryl sagas are really finished! At a meeting of the Society of Toxicology in Dallas in February 1988, Dr. H. V. Aposhian, University of Arizona (and a Rochester graduate) discussed successful removal of ^{210}Po with some newer sulfhydryl agents (Aposhian et al. 1988). In private communications to this author, he also cited the growing number of contamination incidents arising from leakage of polonium from static eliminator devices used in industry. For example, the *New York Times* of February 11, 1988, described the addition of "three more plants" to a growing list of incidents. None of them involved personal injury but have stimulated vigorous clean-up and preventive activities. Incidentally, it is stated that over twenty thousand of the static eliminator devices are in use. Those in plants producing food, drugs, or cosmetics have been recalled (in part, at least).

This resurgence of polonium's well-known tendency to escape from confinement has stimulated also more experimental work on decorporation. Aposhian et al. (1987) tried DMPS (2,3-dimercapto-1-propane-sulfuric acid Na-salt), DMSA (meso-dimercapto succinic acid), and DMPA (N-2,3 dimercapto propyl phthalamidic acid) for comparison with older agents. These are less toxic than BAL, more water soluble, and more effective. Studies on tissue distribution and excretion of polonium and survival times of treated rats showed all to be considerably better than a saline control, with DMPA the most promising. Studies on mechanisms are under way since it is thought that DMPA may have a more extensive intracellular distribution.

(b) Some of these are used in mixtures as indicated: TPHA-tetraethylenepentaamine heptaacetic acid; DTPP-diethylenetriaminepentamethylphosphonic acid; TH-tetracycline hydrochloride; BSA-1,2-dihydroxybenzene-3,5-disulphonic acid; NSA-1-(1-hydroxy-4 methyl-2-phenylazo)-2-naphthol-4-sulphonic acid; UM- β -methylumbelliferone; DFOA-desferrioxamine 8-methane sulphonate.

(c) We will use this term regularly, even though the purpose may sometimes be to prevent incorporation. We will use "decontamination" only in connection with the treatment of wounds.

TABLE 19.4. Systemic Treatment of Intravenously Injected Transuranium Elements in Rats (Dose and Time Effect). [Author, date, and location in bold.]

Radionuclide (route of entry)	Chelate (route of entry)	Treatment			Period of Observa- tion	TU Retention (% of control)			
		Dose per Treatment (mmol · kg ⁻¹)	No. of Treat- ments	Time after TU Injection		Skeleton	Liver		
Taylor and Sowby 1962 - Sutton									
²³⁹ Pu citrate (i.v.)	DTPA (i.p.)	0.75	1	6 h	21 d	20	40		
		1.5		6 h		12	31		
		3.0		6 h		11	27		
		7		6 h, 1 - 4, 7, 14 d	21 d	16	32		
		1.5	3	1, 24, 48 h		10	7		
	TTHA (i.p.)	5		7 - 11 d		46	22		
				7 - 11 d	28 d	49	28		
				7 - 11 d		99	91		
		²⁴¹ Am citrate (i.v.)	DTPA (i.p.)	3.0	3	1 h, 7, 14 d	21 d	17	0.5
						6 h, 7, 14d		26	0.8
	EDTA (i.p.)	9		7 - 11 d, 14 - 17 d		51	0.1		
				14 - 17 d		76	0.2		
Taylor 1967 - Sutton									
²³⁹ Pu citrate (i.v.)	DTPA (i.p.)	0.05	3	1, 5, 24 h	7 d	9	7		
	DFOA (i.p.)			1, 5, 24 h		10	33		
²⁴¹ Am citrate (i.v.)	DFOA (i.p.)	0.15	2	0.5, 22 h	28 d	115	106		
				7 - 8 d		87	106		
				7 - 8 d		43	12		
²³⁹ Pu nitrate (i.v.)	DTPA (i.p.)	0.05	3	0.5, 6, 24 h	21 d	9	36		
	DFOA (i.p.)			0.5, 6, 24 h		37	68		
	DTPA (i.p.)	0.15	1	40 min	28 d	9	17		
	DFOA (i.p.)			40 min		21	47		
	DFOA (i.p.)			24 h		67	68		
	DTPA (i.p.)	3		7 - 9 d		46	17		
	DFOA (i.p.)			7 - 9 d		83	100		
	²⁴⁴ Cm nitrate (i.v.)	DFOA (i.p.)	0.05	3	0.5, 6, 24 h	21 d	62	79	
0.15			1	24 h or 48 h		70	123		
Taylor, Chipperfield, and James 1971 - Sutton									
²³⁹ Pu nitrate (i.v.)	TH (i.p.)	5.0 mg	5	4,3,2,1,0 d before	4 d	60	89		
²⁴¹ Am nitrate (i.v.)						111	73		
²³⁹ Pu nitrate (i.v.)		10.0 mg	1	simultaneously		73	78		
					5 h		100	108	
Fried et al. 1959 - Argonne									
²³⁹ Pu citrate (i.v.)	EDTA (i.p.)	0.8	6	6,12,21,22,25,26 d	27 d	72	140		
	DTPA (i.p.)			6,12,21,22,25,26 d		63	21		
	BAETA (i.p.)	0.7				77	22		
Markley, Rosenthal, and Lindenbaum 1964 - Argonne									
²³⁹ Pu citrate (i.v.)	DTPA (i.p.)	0.6	3	3,6,9 d	12 d	54	~12		
(92% ultrafiltrable)									
²³⁹ Pu citrate (i.v.)						53	100		
(15% ultrafiltrable)									
Smith 1958 - Richland									
²³⁹ Pu citrate (i.v.)	EDTA (i.p.)	~1.5	1	1 h	2 d	70	13		
²³⁹ Pu citrate (i.v.)	DTPA (i.p.)			1 h		54	30		
	EDTA (i.p.)		(25)	38 - 62 d	64 d	81	67		
	DTPA (i.p.)			38 - 62 d		51	13		
Smith 1963 - Richland									
²³⁹ Pu citrate (i.v.)	BSA (i.p.)	1.5	1	1 h	5 d	14	18		
	NSA (i.p.)					33	26		
	UM (i.p.)					69	135		
	DTPA (i.p.)	1.5	1			17	3		
²³⁹ Np citrate (i.v.)	DTPA (i.p.)					80	40		
²³⁷ Np citrate (i.v.)	DTPA (i.p.)					70	40		

TABLE 19.4. Continued

Radionuclide (route of entry)	Chelate (route of entry)	Treatment				Period of Observa- tion	TU Retention (% of control)	
		Dose per Treatment (mmol · kg ⁻¹)	No. of Treat- ments	Time after TU Injection	Skeleton		Liver	
Smith 1964 - Richland								
²³⁹ Pu citrate (i.v.)	DTPA (i.p.)	0.5	3	1,5,24 h	5 d	5	7	
	DFOA (i.m.)	0.5				5	7	
	DTPA + DFOA (i.p.)(i.m.)	0.5+0.5				4	2	
Smith 1972a - Richland								
²³⁸ Pu citrate (i.v.)	Zn-DTPA (i.p.)	1.0	1	1 h	7 d	29	9	
Smith 1972b - Richland								
²⁵² Es nitrate (i.v.)	Ca-DTPA or Zn-DTPA	1.0	1	1 h	7 d	34	7	
	Zn-DTPA (i.p.)	1.0	6	7,9,11,14,16,18 d	24 d	77	13	
Belyaev 1962 - USSR								
²³⁹ Pu citrate (i.v.)	DTPA (i.v.)	0.5	1	simultaneously	3 d	4	14	
	BAETA (i.v.)					33	30	
	DTPA (i.p.)	1.2	1	2 h	3 d	17	11	
	BAETA (i.p.)					26	31	
	DTPA (i.p.)		1	24 h	3 d	67	29	
	BAETA (i.p.)					85	41	
	DTPA (i.p.)	0.5	12	1 - 13 d	16 d	33	10	
	BAETA (i.p.)					41	13	
	DTPA (i.p.)		12	30 - 43 d	45 d	59	19	
	BAETA (i.p.)					73	30	
Belyaev 1965 - USSR								
²³⁹ Pu citrate (i.v.)	DTPA (i.v.)	0.4	1	simultaneously	3 d	3	17	
	DTPP (i.v.)					9	4	
	TPHA (i.v.)					2	14	
	TTHA (i.v.)					0.5	1	
	DTPA (i.p.)		1	2 h	3 d	16	10	
	DTPP (i.p.)					18	18	
	TTHA (i.p.)	0.4	1	2 h	3 d	9	3	
	DTPA (i.p.)		12	1 - 13 d	16 d	34	9	
	TPHA (i.p.)					36	7	
	TTHA (i.p.)					40	4	
	DTPA (i.p.)		12	30 - 43 d	45 d	61	14	
	TPHA (i.p.)					72	24	
	TTHA (i.p.)					71	16	
	Belyaev 1969 - USSR							
²⁴¹ Am chloride (i.p.)	DTPA (i.p.)	1.4	1	24 h	3 d	51	28	
	BAETA (i.p.)			24 h		78	48	
	TH (i.p.)	75 mg	10	24 h		100	42	
	DTPA (i.p.)	0.4	12	1 - 13 d	16 d	22	4	
	DTPA (i.p.)		12	25 - 37 d	45 d	63	11	
Seidel and Volf 1972 - Karlsruhe								
²³⁹ Pu citrate (i.v.)	DTPA (i.p.)	1.0	3	6,8,11 d	13 d	73	20	
	Zn-DTPA (i.p.)					72	23	
²⁴¹ Am citrate (i.v.)	DTPA (i.p.)					72	8	
	Zn-DTPA (i.p.)					77	9	
²⁴² Cm citrate (i.v.)	DTPA (i.p.)	1.0	3			62	8	
	Zn-DTPA (i.p.)					67	9	
Seidel 1975 - Karlsruhe								
²⁴¹ Am citrate (i.v.)	Ca-DTPA (i.p.)	0.03	12	1.5 min, 1 d, then once a week	71 d	15	6	
	Zn-DTPA (i.p.)	0.03	12	1.5 min, 1 d, then once a week	71 d	27	7	

TABLE 19.4. Continued

Radionuclide (route of entry)	Chelate (route of entry)	Treatment			Period of Observa- tion	TU Retention (% of control)	
		Dose per Treatment (mmol · kg ⁻¹)	No. of Treat- ments	Time after TU Injection		Skeleton	Liver
	Ca-DTPA (i.p.)	0.03	1	1.5 min, 1 d	71 d	17	4
	+ Zn-DTPA (i.p.)	0.03	11	then once a week			
	Ca-DTPA (i.p.)	0.03	24	4 d, then once a week	165 d	54	22
	Zn-DTPA (i.p.)	0.03	24	4 d, then once a week	165 d	58	16
		0.1	24	4 d, then once a week	165 d	52	11
Seidel 1976 - Karlsruhe							
²⁵² Cf citrate (i.v.)	Ca-DTPA (i.p.)	0.03	12	1.5 min, 1 d, then once a week	71 d	6	2
	Zn-DTPA (i.p.)	0.03	12	1.5 min, 1 d, then once a week		12	4
	Ca-DTPA (i.p.)	0.03	1	1.5 min, 1 d, then	165 d	7	3
	+ Zn-DTPA (i.p.)	0.03	11	once a week			
	Ca-DTPA (i.p.)	0.03	24	4 d, then once a week		44	20
	Zn-DTPA (i.p.)	0.03	24	4 d, then once a week		50	17
Gemenetzi 1976 - Karlsruhe							
²³⁹ Pu citrate (i.v.)	Ca-DTPA (i.p.)	0.03	24	4 d, then once a week	172 d	86	43
	Zn-DTPA (i.p.)	0.03				89	47
		0.1				70	36
Volf and Gemenetzi 1977 - Karlsruhe							
²³⁹ Pu citrate (i.v.)	Ca-DTPA (i.p.)	0.03	1	1.5 min	36 d	13	12
	+ DFOA (i.p.)	0.03	2	1 d		6	9
			6	1.5 min, 1 d, then once a week		6	10
	Ca-DTPA (i.p.)	0.03	6	1.5 min, 1 d, then once a week		18	12
	Zn-DTPA (s.c.)	0.1	20	4 d, then 5 times a week		49	17
Takada and Volf 1977 - Karlsruhe							
²⁴² Cm citrate (i.v.)	Ca-DTPA (i.p.)	0.03	1	1.5 min	7 d	21	12
			1	1 d	8 d	38	27
			1	1.5 min	7 d	86	52
			1	1 d	8 d	85	46

EDTA = ethylenediaminetetraacetic acid

DTPA = diethylenetriaminepentaacetic acid

TTAA = triethylenetetraamine hexaacetic acid

TPHA = tetraethylenepentaamine heptaacetic acid

DTPP = diethylenetriaminepentamethylphosphonic acid

BAETA = bis di(carboxymethyl)amino diethylether

TH = tetracycline hydrochloride

BSA = 1, 2-dihydroxybenzene-3,5-disulphonic acid

NSA = 1-(1-hydroxy-4 methyl-2-phenylazo)-2-naphtol-4-sulphonic acid

UM = β -methylumbelliferone

DFOA = desferrioxamine 8-methane sulphonate

Substances 1-5 were administered as calcium-sodium chelates, unless stated otherwise.

Source: Modified from Volf 1978, Table VIII.

Systemic treatments of transuranics given by intraperitoneal as well as intravenous injection and in species other than the rat are given in table 19.5, also modified from Volf (1978). Still further experience with animal species and age as variables, as well as the route of administration, is given in table 19.6.

TABLE 19.5. Systemic Treatment of Transuranium Elements in Mice and Other Species. [Author, date, and location in bold.]

Animal Species	Radionuclide (route of entry)	Chelate (route of entry)	Treatment			Period of Observation	TU Retention (% of control)	
			Dose per Treatment (mmol · kg ⁻¹)	No. of Treatments	Time after TU Injection		Skeleton	Liver
Schubert et al. 1961 - Argonne								
Mouse	²³⁹ Pu citrate (>90% ultrafiltrable) (i.v.)	Ca-DTPA (i.p.)	1.0	18	3 d, then daily	21 d	44	3
	²³⁹ Pu citrate (~65% ultrafiltrable) (i.v.)			12	3 d, then daily	15 d	61	67
Rosenthal and Lindenbaum 1964 - Argonne								
Mouse	²³⁹ Pu citrate (i.v.) (90% ultrafiltrable)	DFOA (i.p.)	0.5	11	3-13 d	14 d	71	85
Rosenthal et al. 1969 - Argonne								
Mouse	²³⁹ Pu citrate (i.v.) (82% ultrafiltrable)	DTPA (i.p.)	1.0	12	6 d, then once every 3 d	42 d	50	6
			0.6				56	6
			0.2				50	10
			0.1				63	12
			0.02				77	25
Volf and Seidel 1974 - Karlsruhe								
Rat	²³⁹ Pu citrate (i.p.)	Zn-DTPA (i.p.)	0.1	6	4, 7, 11, 18, 25, 32 d	39 d	76	40
Hamster			0.1				97	49
Rat			0.01				96	62
Hamster			0.01				111	93
Rat	²⁴¹ Am citrate (i.p.)	Zn-DTPA (i.p.)	0.1				63	15
Hamster			0.1				75	42
Rat			0.01				75	30
Hamster			0.01				83	48
Lloyd et al. 1976 - Utah								
Dog	²⁴¹ Am citrate (i.v.)	Ca-DTPA (s.c.)	0.03	7 (35)	2 weeks, then 1 - 5X daily	21 d	92	77
		Zn-DTPA (s.c.)	0.03	7 (35)	2 weeks, then 1 - 5X daily		114	35
				~100 (500)	2 weeks, then 1 - 5X daily	2 a	28	0
Smith et al. 1961 - Richland								
Pig	²³⁹ Pu citrate (i.v.)	DTPA (i.v.)	~0.3	1	simultaneously	6 d	10	3
Cohen, Guilmette, and Wrenn 1974 - New York								
Baboon	²⁴¹ Am citrate (i.v.)	Ca-DTPA (i.v.)	0.03	11		1.5 months	63	10

DTPA = diethylenetriaminopentaacetic acid (calcium trisodium salt)
Zn-DTPA = diethylenetriaminopentaacetic acid (zinc trisodium salt)
TH = tetracycline hydrochloride

DTPA = diethylenetriaminopentaacetic acid (calcium trisodium salt)

Zn-DTPA = diethylenetriaminopentaacetic acid (zinc trisodium salt)

TH = tetracycline hydrochloride

Source: Modified from Volf 1978, Table IX.

TABLE 19.6. Chelate Effectiveness as Influenced by Animal Species and Age as Well as by the Radionuclide and Route of its Administration. [Author, date, and location in bold.]

Animal Species	Radionuclide (route of entry)	Ca-DTPA (i.p.)		TU Retention (% of control)		
		Dose (mmol·kg ⁻¹)	Time after TU Injection	Skeleton	Liver	Kidneys
Seidel 1977 - Karlsruhe						
Rat	²⁴¹ Am (i.v.)	1.0	24 h	63	11	63
Syrian hamster				75	36	47
Chinese hamster				77	16	11
Rat	²⁵² Cf (i.v.)	1.0	24 h	60	15	—
Syrian hamster				60	29	—
Chinese hamster				65	15	—
Smith 1970a - Richland						
Rat (adult)	²³⁹ Pu (i.v.)	1.5	1 h	9	5	17
Smith 1970a - Richland						
Rat (weanling)			1 h	6	2	31
Rat (1 day old)			1 h	6	18	42
			1 d	15	18	48
			10 d	38	44	151
Volf and Seidel 1974 - Karlsruhe						
Rat	²³⁹ Pu (i.v.)	0.1 (6X)	4 - 32 d	73	33	33
Syrian hamster				89	38	32
Rat	²⁴¹ Am (i.v.)	0.1 (6X)	4 - 32 d	59	20	59
Syrian hamster				82	46	49
Seidel and Volf 1975 - Karlsruhe						
Rat	²³⁹ Pu (i.v.)	0.03	1.5 d	46	37	47
	²⁴¹ Am (i.v.)			72	31	58
	²⁵² Cf (i.v.)			58	23	42
Seidel 1976 - Karlsruhe						
Rat	²⁴¹ Am (i.v.)	0.03	1.5 min	28	9	24
	²⁴¹ Am (i.m.)			8	6	27

Source: Modified from Volf 1978, Table X.

No one can say that this subject has not been adequately studied in animals! Consider also that the above tabulations refer only to systemic burdens of the radionuclides received parenterally. Behavior after intramuscular injection to simulate material entering from a wound will be considered separately. Note that, despite the volume of work, only a relatively few laboratories are involved: for the United States, Pacific Northwest Laboratory (PNL) (Richland, Washington); New York University (NYU); ANL (Chicago); and the University of Utah.^(a)

The figures of prime importance in these tables are, of course, the retention in tissues. A few conclusions can be drawn.

(a) Work in other countries is emphasized more in the tables shown here than has been our custom because of space limitations in this book. It has been a highly international enterprise.

1. Very considerable reductions of plutonium burdens can be effected if treatment is given early.
2. Ca-DTPA and BAETA are more effective than EDTA for plutonium.
3. The iron chelator, DFOA (see section III), is quite effective for plutonium, very much less so for americium and the others.
4. The less toxic Zn-DTPA (see later section) is less effective than Ca-DTPA for early treatment, whereas DFOA, TTHA, and BAETA are slightly superior.
5. Many combinations of dose and time have been tried. A more or less standardized procedure has been worked out and will be discussed in the section entitled "Experience in Man."
6. Species differences are seen. For example, the liver retains the transuranic elements longer in hamsters, dogs, and some monkey species than in mice and rats. Americium removal from Chinese hamster liver is more like that from rat than is that from the Syrian hamster. DTPA can remove quite different amounts of ^{241}Am from kidney in different species, even though excretion by untreated animals is about the same in all rodent species tried.
7. Actual removal rates are not always in line with the effective stability constants of the complexes in vitro.
8. Ca-DTPA administered early reduces retention of transuranics in rat bone in the order plutonium, californium, americium, curium.

Much of the preliminary work was done at Hanford and Los Alamos. As early as 1962, Ballou gave what he termed was a preliminary evaluation of the effectiveness of several chelating agents, viz., DTPA, TTHA (see table 19.2), and two strikingly similar substances, aminoethyl cyclohexyldiamine tetraacetic acid (ACDHA) and aminoethoxycyclohexylamine tetraacetic acid (ACHTA). The effectiveness of the various agents was quite different, for plutonium removal at least, despite similarities of chemical structure; ACHDPA and ACHTA were less effective than DTPA or TTHA. The early studies of Foreman at Los Alamos have already been cited (Foreman 1950, 1953, 1954, 1955).

Of further interest is work done at Richland on the removal of plutonium from the neonatal rat by Ca-DTPA (Smith and Sullivan 1978). Oral and parenteral routes were about equally effective, with some indication that absorption of DTPA is more facile from the neonatal rat gut. Other considerations regarding use of chelators in neonates will appear in section VI.

It was especially hoped that a chelating agent could be found that was effective when given orally. This would greatly simplify treatment. Using work of Ballou and colleagues (Ballou 1962a,b; Ballou and Palotay 1966) at Richland and of Taylor and Sowby at Sutton, in the United Kingdom (1962), as a basis, Volf (1978) concludes that only TTHA (triethylenetetraamine hexacetic acid) was equally effective when given orally as when given intraperitoneally.^(a)

Turning to intramuscular and simulated wound sites, the following quotation from Volf (1978) capsulizes the animal studies:

Until recently, considerable uncertainty existed about the route, dosage and rate of administration of the chelating agents in treating contaminated wounds and it was even pointed out that the treatment might induce enhanced absorption and subsequent deposition of the radionuclide in the body organs. It was, however,

(a) In much later work, Taylor and Volf (1980) demonstrated that this finding applied only to fairly high doses. If the chelators were given in low concentration in drinking water, DTPA proved equal to TTHA for plutonium and americium in rats.

suggested that even if absorption of the TU was enhanced, the systemic burden would not increase and even could be substantially lower than without treatment. This view is supported by the fact that TU injected intramuscularly as chelates with DTPA are absorbed almost completely and there is a minimal uptake of translocated TU by the organs, indicating a high stability of TU-DTPA *in vivo*.

Assuming that the effectiveness of DTPA in removing TU from a simulated puncture wound depends primarily on the local molar ratio of DTPA/TU and that DTPA excess can much more easily be achieved by local treatment with DTPA, a chelate injection directly into or close to the TU deposit should be more effective than the systemic treatment. This could indeed be proven experimentally for ^{239}Pu . Similar results have been reported for removal of ^{239}Pu by local injection of DFOA and for removal of ^{253}Es by Zn-DTPA. . . . The importance of ensuring infiltration of the ^{239}Pu deposit by the DTPA is evident from the greater consistency in enhancement of ^{239}Pu translocation achieved by the same chelate dose in a larger volume of solution. However, using a high-pressure spray-injector offers no advantage.

The local effectiveness of Ca-DTPA can be increased by combining it with sodium citrate or with DFOA: Up to about 90% of ^{239}Pu , injected intramuscularly as nitrate, could be removed by treatment 1 hour after administration and about 30% of the ^{239}Pu were removed from the simulated wounds even when treatment was delayed for as long as 3 weeks after contamination. Several other chelate combinations (DTPA plus tartrate, lactate, pyruvate or chinolinate, DFOA plus citrate) were less effective than DTPA or DFOA alone or even increased deposition of translocated ^{239}Pu in the organs. The enhanced effect of some of the combined chelating agents might be due to formation of mixed ligand complexes of plutonium.

It might be concluded that DTPA represents a useful means for supporting surgical therapy of TU-contaminated wounds. Systemic administration of DTPA would mainly reduce the uptake of translocated TU by the organs, whereas local chelate treatment with DTPA or with a suitable combination of chelates would be able to reduce the wound deposit, provided TU are present in a chelatable form, such as TU nitrate. It should be stressed that in large animal species as well as in man the chelating agent administered locally would be effective even if administered at a lower dose than that recommended for the systemic therapy; the local chelate injection should, therefore, be supplemented by a systemic one in order to ensure chelation of TU possibly absorbed into blood in a non-chelated form.

The use of DTPA therapy for the oxide form of ^{239}Pu in a contaminated wound appears to be of limited value. In dogs implanted with air-oxidized ^{239}Pu the only effect of systemic Ca-DTPA was seen in the kidney, while with high-fired ^{239}Pu oxide a reduction of ^{239}Pu in the skeleton was achieved comparable to that observed with ^{239}Pu nitrate. On the other hand, an enhancement in ^{239}Pu concentration following Ca-DTPA therapy was seen in the lung and thyroid after injection of the oxide forms of ^{239}Pu . However, treatment of ^{239}Pu -oxide deposits probably depends a lot on the particle size. In rats, the locally administered Ca-DTPA was capable of diminishing an intramuscular deposit formed by small ^{239}Pu -dioxide particles (<4 nm diameter), which appear *in vivo* even more soluble than a ^{239}Pu -nitrate deposit.

The rapid translocation of ^{239}Pu from a subcutaneous implantate to the proximal lymph node indicates the possibility of removing the latter, i.e. a therapeutic **lymphadenectomy**. However, in comparison with intact dogs, the liver, spleen and hepatic lymph node in the lymphadenectomized animals accumulated greater burdens of ^{239}Pu , which probably occurred before the residual lymph nodes began to function efficiently. Thus, in principle the therapeutic value of a lymphadenectomy for the management of ^{239}Pu -contaminated wounds could be improved mainly by chelation therapy and/or excision of the contaminated wound to minimize the ^{239}Pu reservoir.

(Volf 1978, pp. 33 and 37)

A summary table showing a comparison of systemic and local treatments of intramuscular deposits of transuranium elements in rats illustrates these statements (table 19.7).

TABLE 19.7. Systemic Treatment of Intramuscularly Injected Transuranium Elements. [Author, date, and location in bold.]

Radionuclide (route of entry)	Chelate (route of entry)	Treatment			Period of Observa- tion	TU Retention (% of control)		
		Dose per Treatment (mmol · kg ⁻¹)	No. of Treat- ments	Time after TU Injection		Injection Site	Skeleton	Liver
Parker, Low-Beer, and Isaac, 1962 - Richland								
²⁴¹ Am citrate (i.m.)	DTPA (i.p.)	~0.1	4	2 h, 1 - 3 d	4 d	50	56	<1
		~0.1	10	2 h, 1 - 4 d 7 - 11 d	14 d	25	46	<<1
²⁵² Cf citrate (i.m.)		~0.1	4	2 h, 1 - 3 d	4 d	50	61	<1
		~0.1	10	2 h, 1 - 4 d 7 - 11 d	14 d	20	63	<<1
Taylor, Chipperfield, and James 1971 - Sutton								
²³⁹ Pu nitrate (i.m.)	TH ^a (i.p.)	10.0 mg	4	0 - 4 d	6 d	111	123	109
	TH+DTPA (i.p.)	5.0 mg + ~0.5		0 - 4 d		48	12	13
	DTPA (i.p.)	~0.5		0 - 4 d		47	9	11
Nénot, Morin, and Lafuma 1970 - Fontenay-aux-Roses								
²⁴² Cm nitrate (i.m.)	DTPA (i.m.)	0.1	4	1, 6, 11, 16 d	20 d	37	30	5
Nénot, Morin, and Lafuma 1971a,b - Fontenay-aux-Roses								
²⁴¹ Am sulphate (i.m.)	DTPA (i.m.)	0.1	13	1 d, then once a week	90 d	56	7	13
²⁴¹ Am nitrate (i.m.)	DTPA (i.m.)	0.1	13	1 d, then once a week		30	8	3
Nénot et al. 1972 - Fontenay-aux-Roses								
²⁴² Cm nitrate (i.m.)	DTPA (i.m.)	0.1	6	20 d, then twice a week	40 d	89	49	11
			20		90 d	50	62	4
			30		120 d	52	40	2
²³⁸ Pu nitrate (i.m.)	DTPA (i.m.)	0.1	6		40 d	33	72	23
			20		90 d	27	50	9
			30		120 d	28	37	17
Morin, Nénot, and Lafuma 1972 - Fontenay-aux-Roses								
²³⁸ Pu nitrate (i.m.)	DTPA (i.m.)	0.1	5	1 d, then twice a week	30 d	13	7	
			15	21 d, then twice a week	120 d	38	15	
Morin, Nénot, and Lafuma 1974 - Fontenay-aux-Roses								
²⁵² Cf nitrate (i.m.)	DTPA (i.m.)	0.1	3	1 d, then twice a week	8 d	50	57	13
			5		15 d	33	38	5
			9		30 d	21	24	3
			17	1 d, then twice a week	60 d	20	25	—
	DTPA (i.m.)	0.1	5	3 d, then twice a week	35 d	26	71	26
			9		49 d	39	54	10
			17		77 d	25	42	5
			27		112 d	47	47	5

Rat experiments with the exception of that performed by Parker et al. who used mice.

^a TH = tetracycline hydrochloride.

Source: Modified from Volf 1978, Table VII.

Durbin (1973), in her monumental review of all the biomedical work to 1972 on the transplutonic elements, considered the status of therapy. She cites a few experiments not contained even in the Volf review (tables 19.4 through 19.7). These concerned ^{241}Am , ^{253}Es , and ^{252}Cf , which are shown in table 19.8 modified from Durbin's paper. The chelating agent was DTPA.

TABLE 19.8. Experiments Using DTPA to Promote Excretion of Promptly Deposited Trivalent Actinides in Rodents, and Amount of Nuclide Remaining in Bone after Treatment. [Author, date, and location in bold.]

Isotope and Route of Administration(a)	Length of Study (days)	DTPA Treatment			Total DTPA Given (mM/kg)	Amount of Nuclide in Bone (% of control)
		Treatment Schedule (time after nuclide injection)	No. of Treatments	DTPA per Treatment(b) (mM/kg)		
— STUDIES USING RATS —						
Sowby and Taylor 1960 - U.K.						
²⁴¹ Am citrate, i.v.	21	1 hr, 7, 14 d	3	3.0	9.0	17.5
	21	6 hr, 7, 14 d	3	3.0	9.0	25
	21	7, 14 d	2	3.0	6.0	50
Foreman 1962 - Los Alamos						
²⁴¹ Am citrate, i.v.	30	2 hr, 1-29 d	30	0.46	13.8	17(c)
	30	2 m, 1-29 d	30	0.028, s.t.	0.84	33.8(c)
	30	7-29 d	23	0.46	10.6	36(c)
	30	14-29 d	16	0.46	7.4	59(c)
²⁴¹ Am citrate, i.t.	30	2 hr, 1-29 d	30	0.46	13.8	21(c)
	50	2 hr, 1-49 d	50	0.46	23.0	14.3(c)
Taylor and Sowby 1962 - U.K.						
²⁴¹ Am citrate, i.v.	21	7-11, 14-17 d	9	3.0	27.0	50.5
Belyaev 1969 - USSR						
²⁴¹ AmCl ₃ , i.p.	3	1 d	1	1.5	1.5	52
	16	1-13 d	13	0.41	5.7	22
	40	25-37 d	13	0.41	5.7	63
Seidel and Volf 1972 - West Germany						
²⁴¹ Am citrate, i.v.	13	6, 8, 11 d	3	1.0	3.0	77
²⁴² Cm citrate, i.v.	13	6, 8, 11 d	3	1.0	3.0	67
Smith 1972b - Richland						
²⁵³ Es(NO ₃) ₃ , i.m.	21	1 h, 1-3, 5, 7, 9, 12, 15, 17 d	10	0.33	3.3	42.3
Nénot, Morin, and Lafuma 1971b - France						
²⁴¹ Am(NO ₃) ₃ , aer.	40	20 d, 2/week	6	0.12, i.m.	0.72	82
	90		20	0.12, i.m.	2.4	42
	124		30	0.12, i.m.	3.6	26
— STUDIES USING MICE —						
Parker, Low-Beer, and Isaac 1962 - Richland						
²⁴¹ Am citrate, i.m.	4	2 h, 1-3 d	4	0.11	0.44	34
	14	2 hr, 1-4, 7-11 d	10	0.11	1.10	34

TABLE 19.8. Continued

Isotope and Route of Administration ^(a)	Length of Study (days)	DTPA Treatment			Total DTPA Given (mM/kg)	Amount of Nuclide in Bone (% of control)
		Treatment Schedule (time after nuclide injection)	No. of Treatments	DTPA per Treatment ^(b) (mM/kg)		
²⁵² Cf citrate, i.m.	4	2 hr, 1-3 d	4	0.11	0.44	46
	14	2 hr, 1-4, 7-11 d	10	0.11	1.10	38.5
Parker et al. 1972 - Richland						
²⁵¹ Es citrate, i.m.	1	2 hr	1	0.11	0.11	76.5
	4	2 hr, 1-3 d	4	0.11	0.44	68.5
	14	2 hr, 1-4, 7-11 d	10	0.11	1.10	50
(a) i.v., intravenous; i.t., intratracheal; i.m., intramuscular; i.p., intraperitoneal; s.t., stomach tube; aer., aerosol.						
(b) DTPA administered by intraperitoneal injection unless otherwise specified.						
(c) Based on whole-body measurement at 30 days postinjection; at that time liver and soft tissues have been cleared.						

Source: Modified from Durbin 1973. Reprinted with permission of Springer-Verlag, New York, copyright 1973.

The amount of the radionuclide remaining in bone, as a percentage of the control, is satisfyingly reduced by the treatment in most cases. The disappointments appear largely when the treatment time is short, but there is considerable variability among the experiments. The aerosol treatment (Nénot, Morin, and Lafuma 1971a,b) seemed to require the longest period of use. A slow release implant technique for Zn-DTPA has been devised by Calder et al. at Utah (1978). Further work at Utah considers the variables of form of plutonium, frequency of administration, etc. (Lloyd et al. 1978; Taylor et al. 1978).

Not shown in the tabular material is the fact that fasting had little or no influence on effectiveness of a chelator like DTPA on excretion of plutonium, nor did it change the tissue distribution (Sanders and Meier 1973).

It is clear from the information cited in this section on actinide therapy that the chelators in the EDTA, DTPA class are much more effective than most of the other modalities we have discussed thus far for decorporation of actinide-type elements. Also, the transplutonium elements appear to be transportable to a considerable degree, frequently more easily than plutonium.

b. Reduction of Biological Effects

In considering Hursh's work on BAL, we lauded his extension of the observations beyond the increase in excretion and redistribution among the tissues to measures of relative effects. We commented that this ultimate test of the usefulness of therapy has been notably absent in much of the experimental work on chelation therapy. This has been true, unfortunately, of the work with actinides as well.^(a) In Volf's review (1978), out of 353 references, only 3 concern studies directed toward evaluating the potential reduction in toxicity of the

(a) Dr. Walter Weyzen, who was program manager of the cognizant section in the Department of Energy, often remarked that the goal of chelation research should be the reduction of risk, not just the removal of radioactivity (Mays et al. 1981).

deposited actinide elements.^(a) It now appears that enough work has been done on determining the reduction in effects to prove that such really does occur. Work is continuing, most of it abroad.

We should take note of the reasons a positive result (i.e., reduction in effect) would not inevitably follow the reduction in tissue burdens. The Karlsruhe school has pointed out the forces that might operate against a therapeutic gain. First, tumor incidence reaches a distinct maximum as a function of the amount of deposited radionuclide. This reflects the vectors of carcinogenesis on the one hand and cell killing on the other. Conceivably, a reduction in bone deposition could increase tumor production if the amount of radionuclide present originally was beyond the maximum, i.e., in the region where cell killing overbalanced carcinogenesis. Similarly, the net result might be no effect at all. Obviously, delayed treatment would be expected to have less effect on tumor incidence just as it has on decorporation. Examples exist of differences consistent with these ideas (Volf 1978).

To illustrate clearly therapeutic end-results, we will examine two instances of toxicity measurements with ^{239}Pu . The first concerns DTPA given by inhalation after inhalation of plutonium citrate in rats. It is shown in table 19.9.

TABLE 19.9. Effect of DTPA on Subacute ^{239}Pu -Toxicity in Rats

	Controls	Prophylactic DTPA Inhalation
Survival (d)	184	470
Lung dose (rad)	2230	650-950
Skeletal dose (rad)	374	315
Pneumosclerosis (%)		
Light	9	44
Severe	62	10
Nephrosclerosis (%)	21	25
Bone marrow aplasia (%)	21	2

Ca-DTPA (2.4 mg) was inhaled 30 min before a single ^{239}Pu citrate inhalation, resulting in an initial lung burden of $\sim 0.5 \mu\text{Ci } ^{239}\text{Pu/g}$. 75 control and 60 treated rats.

Source: Reset from Volf 1978, Table XIV.

Obviously, the treatment increased survival, reduced the pneumosclerosis from heavy to light, and had a significant effect on bone marrow aplasia. Effects in kidney (nephrosclerosis) were not reduced.

(a) The reasons for this hiatus have never been formally declared. The effects work requires long periods and much larger expenditures per unit of information gained than work on distribution and excretion. Funds for therapy give quicker results if metabolic endpoints are used. Furthermore, reductions in bone and soft-tissue depositions bespeak reductions in toxicity. Nevertheless, we have been surprised before, and there are enough factors tending in opposing directions in this field that concrete proof of a therapeutic gain is clearly needed. It may have come from the experience with man.

The second example concerns tumor incidence in both bone and soft tissue, which was examined in detail for both monomeric and polymeric plutonium by Rosenthal and Lindenbaum (1967) at ANL. A summary is shown in figure 19.6A and B.

FIGURE 19.6A. Cumulative bone tumor incidences, expressed as percent of mice with bone tumors and plotted at 25-day intervals, in mice given monomeric plutonium followed by DTPA for 12 days. (Redrawn from Rosenthal and Lindenbaum 1967. Reprinted with permission of Academic Press, Orlando, Florida, copyright 1967.)

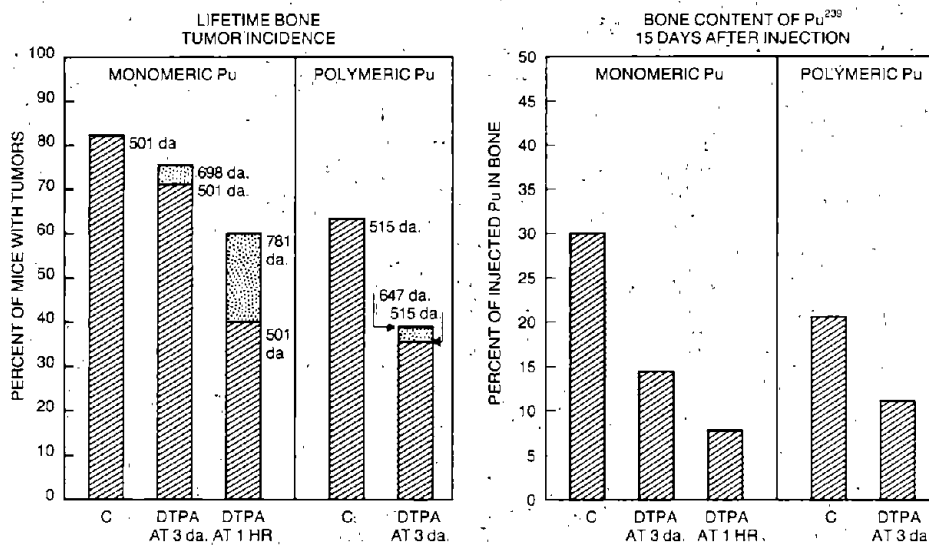
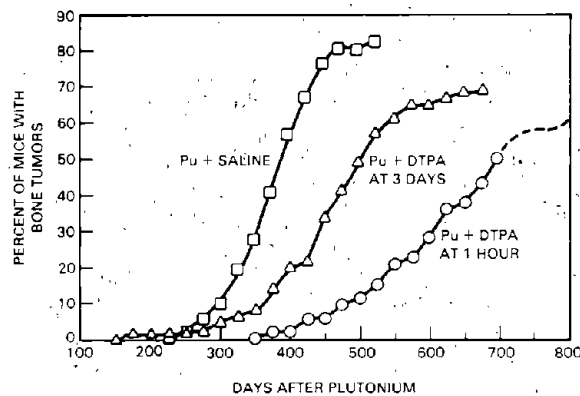


FIGURE 19.6B. Effects of twelve daily intraperitoneal injections of 500 mg of DTPA per kilogram, initiated either 3 days or 1 hr after intravenous administration to mice of either $0.0643 \mu\text{Ci}$ ($\sim 2.6 \mu\text{Ci/kg}$) of monomeric plutonium or $0.0587 \mu\text{Ci}$ ($\sim 2.6 \mu\text{Ci/kg}$) of a polymeric form of plutonium (1.6). Control mice (C) received plutonium and twelve injections of saline solution. Bone tumor incidence in each DTPA-treated group is shown both at the time of death of the last plutonium-control mouse at 501 days for monomeric, and 515 days for polymeric plutonium) and at the time of death of the last treated mouse. The amount of plutonium shown in the bone is that measured in two femurs $\times 10$. (Redrawn from Rosenthal and Lindenbaum 1967. Reprinted with permission of Academic Press, Orlando, Florida, copyright 1967.)

Again, it is clear that time of administration of the chelator is critical. It will be noted that the percentage of animals bearing tumors of bone appeared to be delayed (the principal effect), and total incidence was also reduced somewhat. This was in the mice receiving monomeric plutonium, the most carcinogenic form (figure 19.6A). The lifetime bone tumor incidence is reduced also for polymeric plutonium. A rough correlation to bone content of plutonium can be seen in figure 19.6B. The effects of delay in treatment can be seen in the greater amelioration of effects as well as in the greater reduction of bone content of plutonium with earlier injections (figure 19.6B).

The fact that changes might occur in the microdistribution of the plutonium deposited in bone was demonstrated by Polig (1976a,b) working at Karlsruhe. Autoradiograms confirmed the ideas developed from the bone chemistry, viz., that the chelating agent (Ca-DTPA) brought about the most marked reductions in deposition of the transuranium elements in the areas of newly formed bone, metaphysis and diaphysis, and less reduction in the deposits buried and not as susceptible to removal by these chelating agents. To the degree that the buried deposits are the less important to tumor production, this shift in pattern bespeaks a reduction of effects, perhaps out of proportion to the reduction of bone content.

This small amount of work on reduction of effects does not allow much quantitation. It does indicate that benefits have been demonstrated directly. In retrospect, it appears that the resources expended on fine-tuning of the effects of these chelators on distribution and excretion of radionuclides in a variety of systems and on many dosage regimens may have gone further than the needs of the times. More effort toward obtaining quantitative data on reduction of effect might well have replaced some of the metabolic experiments. It is probably futile to recommend expansion of the effects work now since funding for nearly all work on radionuclide therapy in the United States has been cut off. Nevertheless, the prosecution of such studies should be earmarked for pursuance if, as, and when funding becomes available. The work in progress at Utah thus becomes of special importance.^(a)

c. Removal of Inhaled Actinides

Some major efforts were expended on means of removal of the actinide elements after inhalation and deposition in the lung and accessory respiratory structures. This was concentrated in the laboratories most involved with pulmonary radiotoxicology, especially at Hanford and the Lovelace Foundation Inhalation Toxicology Research Institute (see chapters 8 and 9).

It is more convenient to discuss all aspects of the removal of inhaled radionuclides together. Hence, this important portion of the therapeutic approaches to actinide removal will be postponed to section IV F, except for the small portion included in table 19.9.

2. Use of Main-Line Chelators for Removal of Other Elements

The chelating agents have been tried and used predominantly for the actinide elements. The tabular summaries above testify to this. The laboratories

a) *Note added in proof:* Very recently, the Utah group (Jones et al. 1986) presented clear evidence for a reduction in cancer risk from ²³⁹Pu by chelation therapy. This is a fully quantitative and detailed study in the dog and extends the work in the female mouse by Rosenthal and Lindenbaum shown on page 1619.

concerned were not unaware of the importance of decorporation therapy for other radionuclide groups, but EDTA, DTPA, etc., arrived on the scene at the same time as major concern for plutonium and the actinides, i.e., the potential for a "plutonium economy." Nevertheless, some experimental work was done toward decorporation of radionuclides other than the actinides. This will be reviewed briefly in this section. Frequently, the chelator was only part of a multicomponent mixture.

Most of the work was done in the earlier postwar years, i.e., in the 1950s and 1960s. Much of it was stimulated by the problems initiated by fallout from weapons tests. Probably the best single compendium on the use of the EDTA, DTPA, and similar chelators for decorporation of radionuclides such as strontium, ruthenium, cerium, and rare earths in general is found in the scientific meeting sponsored by the International Atomic Energy Agency-World Health Organization (IAEA-WHO) in Vienna in 1962 (IAEA 1963). It considers both animal work and clinical trials. Our interest here is the experimental work with animals.

Copp and Kavin (1956), working at Berkeley, tried Ca-EDTA for removal of ^{91}Y and ^{90}Sr from rats, including its influence on uptake from wounds. There was reduced absorption from the wound and enhanced urinary excretion in the case of yttrium. The Ca-EDTA had little effect on strontium uptake or removal.

Jenifer Jowsey, a visiting investigator from the United Kingdom working at the University of Chicago (ANL), showed reduced retention of yttrium in bone of rabbits receiving EDTA. She also showed by autoradiography that the yttrium was removed primarily from the metaphyseal trabeculae. Repeated injections prevented the secondary deposition of the radionuclide below the epiphyseal plate usually associated with bone remodeling (Jowsey, 1956).

Cohn (1956), whose work from the NRDL has already been cited, chose ^{91}Y as a prototype for the lanthanide rare-earth group of fission products. He tried a mixture of sodium and calcium EDTA in mice and found greatly increased amounts of yttrium in the excreta, with reduced deposition in liver and muscle. For treatment of radiostrontium, he used BAL in combination with EDTA and also used zirconium with EDTA. The mixtures were used because it was already known that strontium was not much affected by the agents singly. The mixtures were slightly more effective, but the results, using ^{90}Sr , were of marginal biological significance.

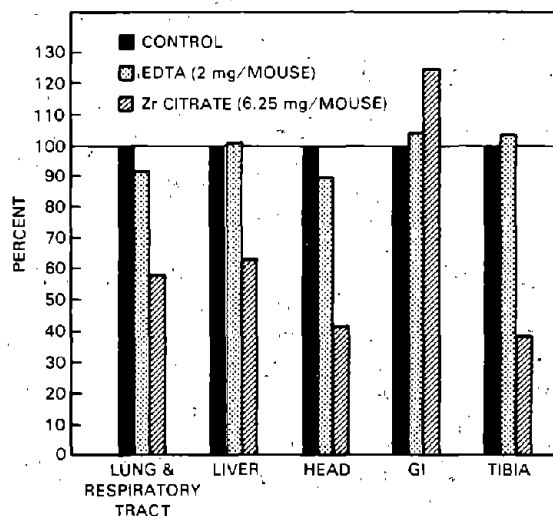
Cohn then turned to three-day-old mixed fission products in a fallout simulant. The work involved a complex protocol whose features and results are shown in figure 19.7A and B taken from Cohn's work. A few treatments increased excretion and reduced somewhat bone and liver deposition of these mixed fission products. Zirconium was clearly better than EDTA in this case. However, the data illustrate vividly how much effect small changes in regimen have on the final result (see also Cohn and Gong 1953).

The Hanford group used primarily the inhalation route and studied ruthenium, iodine vapor, strontium sulfate, and cerium oxide. (As stated above, we will review the inhalation work separately.) Some noninhalation work on animals was done at Hanford on ruthenium (Smith 1965) and promethium (Smith 1970b,c,d), nearly all of it reported in annual progress reports. There was also experimental work on promethium in man (Palmer and Nelson 1970).

Fried and Schubert at Argonne (1961) tried EDTA and DTPA for decorporation of thorium, largely in colloidal form, from rats and mice. The results were marginal.

GROUP	NO. RATS	TREATMENT	TIME	PERCENT INJECTED DOSE**											
				0	10	20	30	40	50	60	70	80	90	100	
				SKELETON				LIVER		SOFT TISSUE		EXCRETA			
A	12	CONTROL	----												
B	6	ZIRCONIUM CITRATE (25 mg as Zr)	PRE-1 HR (IP)												
C	6	ZIRCONIUM CITRATE (25 mg as Zr)	PRE-1 HR (ORAL)												
D	5	ZIRCONIUM CITRATE (25 mg as Zr)	POST-1 HR												
E	5	ZIRCONIUM CITRATE (25 mg as Zr)	POST-3 DAY												
F	5	ZIRCONIUM CITRATE (25 mg as Zr)	POST-7 DAY												
G	6	SODIUM CITRATE (25 mg)	PRE-1 HR												
H	6	SODIUM CITRATE (25 mg)	POST-1 HR												
I	5	SODIUM EDTA (10 mg)	PRE-1 HR												
J	5	SODIUM EDTA (10 mg)	POST-1 HR												
K	6	SODIUM EDTA + Zr CITRATE	POST-1 HR PRE-1 HR												
L	6	SODIUM EDTA + Zr CITRATE	PRE-1 HR POST-1 HR												

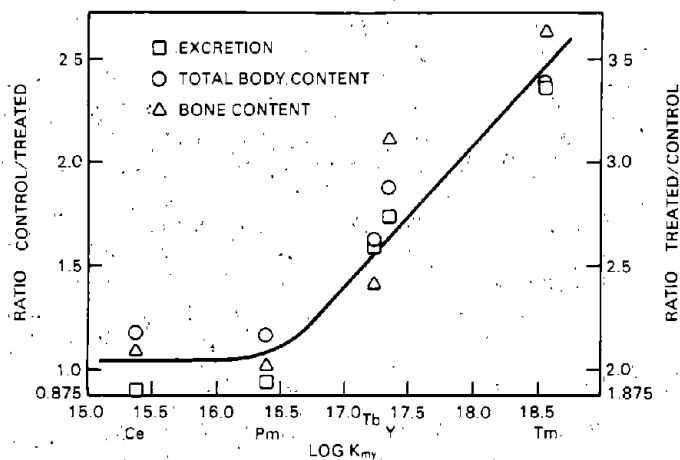
* TIME OF TREATMENT WITH REFERENCE TO MIXED FISSION PRODUCT INJECTION

** ALL VALUES IN PERCENT INJECTED DOSE CORRECTED TO 100% RECOVERY
(ACTUAL INJECTED DOSE RECOVERED: 89-102%)**FIGURE 19.7A.** The effect of chemical agents on the distribution and excretion of injected long-lived fission products. (Redrawn from Cohn 1956.)**FIGURE 19.7B.** Effect of zirconium citrate and EDTA on distribution of fission products in mice exposed to fallout simulant. The ordinate gives the percent of the control amounts in the organ. (Redrawn from Cohn 1956.)

Herta Spencer at the Hines Veterans Hospital in Hines, Illinois, did some animal work with rare earths as a prelude to her quite extensive metabolic studies on man (see Spencer and Rosoff 1963).^(a)

Work at Los Alamos by Harry Foreman's group (Foreman and Finnegan 1957) used deposition and excretion of rare earth elements as a vehicle for analyzing the relationship between the effect of chelating agents in vivo and the stability constants determined in vitro. They used ^{144}Ce , ^{147}Pm , ^{150}Tb , ^{91}Y , and ^{170}Tm , with EDTA as the chelator. In the many symposia we have cited, the physical chemistry of the chelators was a major subject; one we do not have space to describe. There are separate affinity and stability constants for each of the several processes involved. Foreman decided that, for his system, two of the affinity constants were of primary importance, the affinity of EDTA for the various rare earths, and the stability constant of the rare earth natural binding agent complex. In figure 19.8, we see a plot of a derivative of these two constants (plotted as the log of the stability constant for the complex, EDTA-rare earth), which varies with the molecular weight of the rare earth element concerned, against the chelating effectiveness, given as a ratio of control to treated.^(b)

FIGURE 19.8. The relationship of stability constants to chelating effectiveness in the body. Detailed in the text. (Redrawn from Foreman and Finnegan 1957. Reprinted with permission of the American Society of Biological Chemists, Bethesda, Maryland, copyright 1957.)



The rats treated with Ca-EDTA showed real differences in tissue content after treatment at values of the log K_{my} ^(c) above 16.6 or between promethium and terbium. The largest effect was in the long bones and the liver and in the total excretion. The magnitude of the maximum effect on the urine is quite comparable to the effects of EDTA in mobilization of the actinides. Of interest is the fact that the "turnover point" in the curve can be shifted by altering the dose of the chelating agent, i.e., the magnitude of the effect can be altered. (This, of course, reaches a maximum.)

- (a) The texts of the reports cited show only data for man, but there are references from the same laboratory to work with animals.
- (b) Although the figure as presented by Foreman and Finnegan does not so state, it appears from the data that the average effectiveness ratio given is some sort of composite from data on urine, feces, liver, spleen, long bones, and the remainder tissues.
- (c) K_{my} represents the stability constant for the metal and the chelating agent as explained by Foreman and Finnegan (1957).

Earlier work by Foreman, done while he was at Berkeley on a postdoctoral fellowship, compared the effectiveness of EDTA in hastening urinary excretion of ^{91}Y and ^{239}Pu (Foreman 1953). Both radionuclides were mobilized in terms of increases in urinary excretion; the effect on plutonium seeming to be somewhat longer lasting. In neither case, even with a tenfold increase in urinary excretion, was the tissue burden reduced to the extent hoped for.

Foreman postulates from the in-vitro data that chelating agents of the EDTA type would not mobilize strontium or radium because calcium forms a stronger chelate. This prediction has been borne out in animal work already cited, in work abroad, and in the clinical trials.

At the University of Utah, almost all of the work concerns actinides. However, Stover and colleagues (Stover et al., 1958; Stover, Ruhmann, and Atherton 1966) tried EDTA in two dogs that had received ^{228}Th two years previously. There was no enhancement of excretion of the daughter product, ^{224}Ra , but there was a marked effect on urinary excretion of ^{212}Pb . This was not unexpected since the stability constant between lead and EDTA is much higher than that for calcium or radium. Indeed, this fact accounts for the considerable effectiveness of the main-line chelators in decorporation of lead, a story we cannot present but one that took place in many American laboratories before and at the same time we have been describing.

At New York University, primary interests were also in the actinides, especially americium. However, they also studied the effects of Ca-EDTA on mobilization of ^{210}Pb . Using the baboon, they concentrated on oral administration of the chelator. They achieved a doubling of the urinary excretion of ^{210}Pb (Wrenn 1977). (a)

A rather thorough study of the decorporation of radiocobalt was carried out by Fisher and Dunavant at the University of Florida (1978). They were interested in possible contamination incidents with ^{59}Co and ^{60}Co and were concerned that therapeutic measures for these had not been established. One reason for this hiatus was a mistake in the officially promulgated retention time for cobalt in man. The International Commission on Radiological Protection (ICRP) 1959 biological half-life was given as 9.5 days, based on limited animal studies. Later work indicated several components in the retention function with some long-lived fractions that predicted an average biological half-life in man of about seven years. Fisher and Dunavant tried five chelators and chelating mixtures. The old standbys were quite ineffective for decorporation of cobalt. However, a chelator with cobalt integrated into the structure, viz., CoNa_3DTPA reduced the radiocobalt body burden to 66% and the liver burden to 40% of the controls in mice. The reasons for the ineffectiveness of CaNa_3DTPA and ZnNa_3DTPA and the better results with CoNa_3DTPA are considered to lie in the special chemistry of cobalt as a transition metal.

Despite the studies cited, it must be observed that animal work in American laboratories on chelation of radionuclides other than the actinides has been

(a) This experiment was directed at more than the objective of testing the chelator. The NYU group was interested in means of identifying uranium miners with significant skeletal burdens of ^{210}Pb resulting from exposure to radon daughter products. The urinary excretion of lead from skeletal stores is so slow that they used the chelator to provoke excretion and thus help identify miners to be measured by in-vivo scintillation counting. They used the oral route since it was their plan to use it for the miners. It is likely they could have achieved higher excretion rates by parenteral injection of the chelator.

rather sparse. By contrast, rather considerable efforts took place in the United Kingdom, France, and West Germany. Perhaps the most efficient way to enter that literature is through the excellent papers by Nelson (1963) on strontium and by Catsch and Seidl (1963) and Bruce (1963) concerning rare earths and ruthenium. These are in the IAEA symposium already cited. Each of these papers gives a cogent summary of the world's literature.

By contrast, much work was done in American and other laboratories on the effectiveness of the other pharmacological agents and on modifications of diet, particularly on strontium uptake and removal. Also, American laboratories did fairly extensive studies in man toward removal of fission products and rare earths as well as the actinides, as we shall see in section V.

D. Modification of the Main-Line Chelators and Substitutions

1. LICAMs

Recently, there have been developments in compounds with tetracatechoyl ligands (cyclic and linear) and tetracatechoyl amides (CYCAMs or LICAMs). These specific sequestering agents were the result of work by a group of chemists at Berkeley (Weitl et al. 1978; Raymond and Smith 1981). They have low reactivity with divalent metals and thus cause less depletion of these than DTPA.

The effectiveness of these new agents, i.e., one called LICAM-S^(a) in decorporating plutonium has been examined in depth by Durbin et al. (1980). The emphasis in this work was on the effect of variations in the chemical structure and is more detailed than we can present here. The conclusion was that electron donor groups that bind Fe (III) preferentially also bind Pu (IV) efficiently. They bound ²³⁸Pu in valence state IV while it was still in body fluids and effectively prevented further deposition in skeletal tissues of mice. Several of these ligands also prevented deposition in liver, but they could not remove plutonium once deposited in liver. On the other hand, they could remove as much or even more plutonium from the skeleton as an equimolar amount of CaNa₂DTPA. The linear configurations (LICAMs) were somewhat more effective than cyclic configurations (CYCAMs). Acute toxicity was not marked in mice, although some members showed measurable toxicity.

The work was picked up using dogs in collaborative efforts between the groups at Utah (Mays, Bruenger, Lloyd, Taylor, and Wrenn) and the Berkeley group (Durbin and others). The LICAM-S was prepared by the group at Berkeley. They compared effectiveness against both plutonium and americium with results illustrated in table 19.10. The comparison involved Ca-DTPA and two fairly recently synthesized LICAM compounds.^(b)

Obviously, the LICAM-S was somewhat better than Ca-DTPA in terms of reducing whole-body retention of plutonium, but much less effective with americium. A mixture of LICAM-S and Ca-DTPA reduced plutonium retention still further but was about the same as Ca-DTPA alone against americium.

Thus, these compounds show promise for specific uses, but may not be as generally useful as the polyamino-polycarboxylic compounds. Their lack of

(a) N¹, N⁵, N¹⁰, N¹⁴-tetra (2, 3-dihydrox-5-sulfobenzoyl)-tetraazatetradecane.

(b) Modifications of the structure were made to attempt to overcome nephrotoxicity of some of the earlier LICAM compounds reported by F. W. Bruenger at Utah in unpublished observations. The methods of preparation are described in the references given.

TABLE 19.10. Effectiveness of Various Chelating Agents on the Removal of Plutonium and Americium from Beagles

Treatment*	Total-body retention at 7 days	
	Plutonium % \pm S.D.	Americium % \pm S.D.
Untreated	87 \pm 5	89 \pm 6
CaDTPA	29.7 \pm 6.5	20.1 \pm 1.1
LICAM-C	11.8 \pm 0.6	71.6 \pm 2.4
LICAM-S	13.7 \pm 0.6	67.2 \pm 1.5
LICAM-S plus CaDTPA	11.6 \pm 1.3	20.9 \pm 1.2

* 30 μ mole/kg of each agent was injected intravenously at 30 minutes.

Source: Reset from Mays et al. 1981. Reprinted with permission of RD Press, University of Utah, Salt Lake City, Utah, copyright 1981.

binding to essential divalent metals and thus reduced tendency to deplete the body stores of essential metals may be the chief advantage of the LICAM group. *Work on them should be continued.*

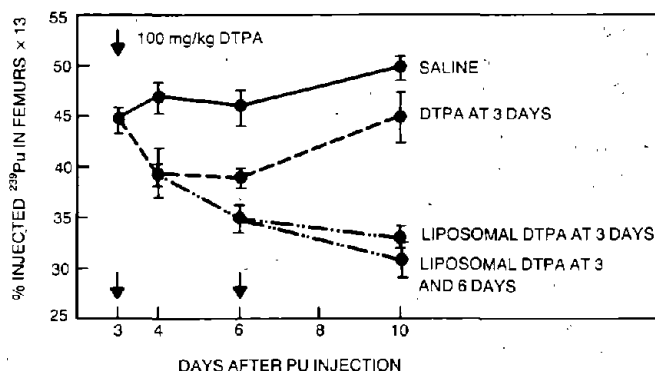
2. Lipophilic Compounds

As work progressed at a number of laboratories on the metabolism of the chelating agents themselves, using compounds labeled with a radioactive tracer, it became clear that a small but significant portion of the agent remained in the body considerably longer than the main portion. (The latter was degraded by metabolic processes in relatively short times—half-period about two hours.) The longer-lasting portion was postulated to be within cells, while the rest remained outside of cells. On this basis, attempts were made to modify the chelators to promote penetration into cells. Increasing the fat solubility is one approach to this end. Hence, "lipophilic compounds" were developed. Since it was also apparent in work at Utah and in the United Kingdom (see chapter 8) that the actinides were associated with lysosomes in rat and dog, at least, the idea gained further credence.

One approach was that taken at ANL by Marcia Rosenthal and colleagues. They (Rahman, Rosenthal, and Cerny 1973; Rosenthal et al. 1975) prepared lipid spherules from lecithin, called liposomes, and encapsulated DTPA within them in bimolecular layers of lipid separated by an aqueous phase.^(a) They used EDTA labeled with ^{14}C for some of the work and demonstrated markedly increased uptake and retention of the agent in liver, spleen, lungs, and bone marrow of mice. They demonstrated improved removal of polymeric plutonium from mouse liver and skeleton and increased urinary excretion. They also found that relatively low doses were as effective as higher doses. A sample of the results is given in figure 19.9, taken from the most successful experiment of

(a) The methods of preparation are described in separate publications cited in the references given.

FIGURE 19.9. Effect of liposome-encapsulated DTPA or of nonencapsulated DTPA on the skeletal content of Pu (the amount in both femurs $\times 13$). Liposome-encapsulated DTPA, 100 mg/kg, was injected intravenously at 3 days, or at 3 and 6 days, after injection of Pu. Nonencapsulated DTPA, was injected intraperitoneally at 3 days after Pu. (Redrawn from Rosenthal et al. 1975. Reprinted with permission of Academic Press, Orlando, Florida, copyright 1975.)



Rosenthal et al. (1975). Relative removal rates were not quite so different in other experiments using different dosage regimens.

Effectiveness with long-standing deposits of plutonium is a matter for conjecture. The Argonne workers tried injections out to twenty-four days after the plutonium was given, but there was no work with the long-term plutonium burdens of interest in many clinical cases. It is with these that the intracellular penetration might make the most difference.

Interest in the intracellular portion of deposited radionuclides and the corresponding intracellular fraction of chelating agents has continued at Argonne, principally in Arthur Lindenbaum's group (Bhattacharyya, Peterson, and Lindenbaum 1978a,b; Bhattacharyya and Peterson 1979). Bhattacharyya, among others, has been interested in penetration of DTPA into liver cells. It may well be that most of the extra plutonium mobilized from liver to bile is handled by intracellular DTPA. It is also clear that chelators can enter macrophages and cells in tissue culture (see, for example, work from Battelle by Sanders and by Robinson et al., quoted by Mays et al. [1981]).

In the United Kingdom, a partially lyophilic derivative of DTPA was developed. It had a structure not too different from the main-line chelators except for very long aliphatic chains, which presumably increased lipid solubility. The substance was named "Puchel," and its structure is shown in figure 19:10, taken from the summary report of Stradling and Bulman (1981).

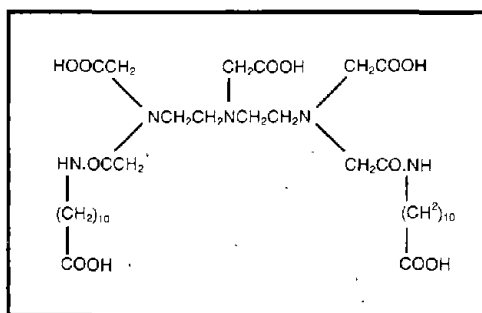


FIGURE 19.10. The structure of Puchel. (Redrawn from Stradling and Bulman 1981. Reprinted with permission of RD Press, University of Utah, Salt Lake City, Utah, copyright 1981.)

As Stradling and Bulman summarized, with earlier literature cited therein, this derivative of DTPA was superior to DTPA in enhancing the clearance of plutonium from the liver of hamsters, even if given up to ten days after the plutonium. Perhaps the most promising area for Puchel is found in its ability to move plutonium and americium from the lungs. Liposomally entrapped DTPA did not seem to have this property.

The mechanisms of action of DTPA and Puchel appear to be quite different. Puchel clears most of plutonium or americium to the feces, while the urine carries most of the DTPA-cleared activity.

The ability of Puchel to decorporate radioelements from bone appears yet to be evaluated.

Neither of these promising compounds, liposomally encapsulated DTPA or Puchel, has reached commercial production^(a) or clinical evaluation as of the time of this writing. As Mays et al. pointed out (1981), the importance of intracellular decorporation and of getting chelators inside cells has only recently been appreciated.^(b) We may see some interesting developments along these lines, although the cutoff of funds for chelation research (see Smith 1981) cannot help but retard new developments.

A summary of animal research aimed at improving the intracellular penetration of DTPA was tabulated by Volf (1978). Some results with transuranic elements (which do not include the more recent work described above) are reproduced as table 19.11.

TABLE 19.11. Attempts to Improve Intracellular Penetration of DTPA. [Author, date, and location in bold.]

Animal Species	Radionuclide (route of entry)	Chelate (route of entry)	Treatment			Period of Observation	TU Retention (% of control)	
			Dose per Treatment (mmol · kg ⁻¹)	No. of Treatments	Time after TU Injection		Skeleton	Liver
Markley 1963 - Argonne								
Mouse	²³⁹ Pu citrate (i.v.) (16% ultrafiltrable)	DTPA (i.p.)	0.74	11	3-13 d	14 d	71	71
		DTPA-ester (i.p.)	0.14				92	75
		DTPA + DTPA-ester (i.p.)	0.63+0.14				68	42
Rosenthal et al. 1975 - Argonne								
Mouse	²³⁹ Pu citrate (i.v.) (35-45% ultrafiltrable)	Ca-DTPA (aqueous) (i.v.)	1.0-2.0	1	3 d	10 d	83	59
		Ca-DTPA (liposomal)	0.05	1				50
			0.1	1				50
			0.2	1			60	43
Stevens et al. 1974 - Utah								
Rat	²⁴¹ Am citrate (monomeric) (i.p.)	Zn-DTPA (aqueous) (i.p.)	0.04	2	12, 20 d	1 mo.	77	7
		Zn-DTPA (liposomal) (i.v.)					84	14

(a) Stradling and Bulman mention negotiations for commercial production of Puchel.

(b) See also new work with thiol compounds cited in section IV B.

TABLE 19.11. Continued

Animal Species	Radionuclide (route of entry)	Chelate (route of entry)	Treatment			Period of Observation	TU Retention (% of control)	
			Dose per Treatment (mmol · kg ⁻¹)	No. of Treatments	Time after TU Injection		Skeleton	Liver
Stevens et al. 1974 - Utah								
(cont.)		DTPA-ester (emulsion) (p.os)					82	22
		Zn-DTPA (aqueous) (i.p.) + DTPA-ester (emulsion) (p.os)					63	7
Stather et al. 1976 - Harwell								
Hamster	²³⁹ Pu nitrate (monomeric) (i.v.)	Ca-DTPA (aqueous) (i.v.)	~0.03	1	1 d	1 mo.	69	80
		Ca-DTPA (liposomal) (i.v.)	~0.03				71	78
Rat	²³⁹ Pu nitrate (monomeric) (i.v.)	Ca-DTPA (aqueous) (i.v.)	~0.03	1	1 d	1 week	79	69
		Ca-DTPA (liposomal) (i.v.)	~0.03				79	76

Source: Modified from Volf 1978, Table XII.

As indicated by the column labeled "TU retention," the success of compounds or combinations intended to increase cellular penetration was greater in the case of liver than for skeleton. This is not surprising since the skeletal binding process involves more complex reactions than simply the question of being within or outside of cells. The increase in effectiveness by going to fat soluble forms is not very consistent.

3. Adjunctive and Mixed-Ligand Therapy

a. Adjunctive Therapy

We will soon review approaches to therapy of deposited radionuclides by methods quite different from the use of chelators. In this section, we will consider briefly additional work in which chelators have been tried in combination with other quite different agents and also work in which chelators or closely related substances have been tried in combination. We will call the first adjunctive and the second mixed-ligand therapy. The reasoning behind some of the combinations will be obvious. In other cases, the *raison d'être* does not stand out. We will try to include a few words of explanation in these latter cases.

Again we can start with a convenient summary table from the book by Volf (1978). In table 19.12, we find a summary of most of the work through the mid-1970s using adjuncts to DTPA. (Some work was done with adjuncts to other chelators, but DTPA was the most used.) This summary suffices for our needs. Obviously, the bulk of the work comes from Argonne and Hanford.

The reasoning behind some of the adjuncts is as follows:

Glucan—from cell walls of yeast. Postulated to facilitate disruption of intracellular aggregates of plutonium and other transuranics in liver. Action demonstrated by autoradiography.

Pyran—facilitates lipid solubility.

Triton—a detergent with a possibly different mode of action, a lysomotropic agent.

The reasoning for the use of urethane and hydroxyquinoline is somewhat obscure.

TABLE 19.12. Effect of Various Factors as Adjuncts to DTPA After Injection of Plutonium. [Author, date, and location in bold.]

Animal Species	Radionuclide (route of entry)	Chelate (route of entry)	Treatment			Period of Observation	TU Retention (% of control)	
			Dose per Treatment (mmol · kg ⁻¹)	No. of Treatments	Time after TU Injection		Skeleton	Liver
Smith 1963 - Richland								
Rat	²³⁹ Pu citrate (i.v.)	DTPA (i.p.)	1.5	1	10 min	5 d	8	2
		UR (i.p.)	1 g	2	2, 1 d before		119	58
		UR+DTPA (i.p.)(i.p.)	1 g + 1.5	2 + 1	2, 1 d before (DTPA: 1 h after)		12	2
		UR (i.p.)	1 g	3	1 h, 1, 2 d		95	98
		DTPA+UR (i.p.)(i.p.)	1.5 + 1 g	1 + 3	1 h, 1, 2 d (DTPA: 1 h)		13	3
		HQ (i.p.)	0.3	1	2 min		45	115
		HQ+DTPA (i.p.)(i.p.)	0.3 + 1.5	1 + 1	2 min + 1 h		13	20
Sanders and Meier 1973 - Richland								
Rat	²³⁹ PuO ₂ (i.p.) (72% ultrafiltrable)	DTPA (i.p.)	~2.5	1	simultaneously	21 d	12	4
		DTPA (i.p.)		3	1 h, 4, 7 d	30 d	16	3
		DTPA+fasting (i.p.)			1 h, 4, 7 d (1-10 d fasting)		17	3
		DTPA (i.p.)		2	14, 21 d		81	32
		DTPA+fasting (i.p.)			14, 21 d (1-10 d fasting)		57	110
Rosenthal, Smoler, and Lindenbaum 1968 - Argonne								
Mouse	²³⁹ Pu citrate (i.v.) (30% ultrafiltrable)	DTPA (i.p.)	1.0	12	5 d, then once every 3 d	41 d	51	59
		Glucan (i.v.)	40 mg				150	69
		DTPA (i.p.)+ Glucan (i.v.)	1.0 + 40 mg				54	43
		DTPA (i.p.)	1.0	16		89 d	30	62
		Glucan (i.v.)	40 mg				125	56
		DTPA (i.p.)+ Glucan (i.v.)	1.0 + 40 mg				29	30
Rosenthal et al. 1973 - Argonne								
Mouse	²³⁹ Pu citrate (i.v.) (14% ultrafiltrable)	DTPA (i.p.)	0.2	3	5-7 d	47 d	51	67
		DTPA (i.p.)+ Glucan (i.v.)	0.2+20 mg		5-7 d		58	45
		DTPA (i.p.)	0.2	6	5-7 d, 47-49 d	90 d	40	58
		DTPA (i.p.)+ Glucan (i.v.)	0.2+20 mg		5-7 d, 47-49 d		41	28

TABLE 19.12. Continued

Animal Species	Radionuclide (route of entry)	Chelate (route of entry)	Treatment			Period of Observation	TU Retention (% of control)		
			Dose per Treatment (mmol · kg ⁻¹)	No. of Treatments	Time after TU Injection		Skeleton	Liver	
Baxter, Rosenthal, and Lindenbaum 1973 - Argonne									
Dog	²³⁹ Pu citrate (i.v.) (87% ultrafiltrable)	DTPA (i.v.)	~0.2	24	6 d, then twice a week	90 d	52	4	
		DTPA (i.v.)+ Glucan (i.v.)	~0.2+15 mg	24+3	DTPA as above, Glucan: 6,34, 62 d		51	4	
Rosenthal et al. 1975 - Argonne									
Dog	²³⁹ Pu nitrate (<0.1% ultrafiltrable) (i.v.)	Ca-DTPA (i.v.)	0.2	24	6 d, then twice a week	3 mo.	37	91	
		Glucan (i.v.)	(15 mg)	3	6,34, 62 d		206	95	
		Ca-DTPA (i.v.)	0.2	24	6 d, then twice a week		67	83	
		+ Glucan (i.v.)	+	3	6,34, 62 d				
Lindenbaum, Rosenthal, and Guilmette 1976 - Argonne									
Mouse	²³⁹ Pu nitrate (i.v.) (45% ultrafiltrable)	Ca-DTPA (i.p.)	0.25	8	5 d, then twice a week	32 d	59	71	
		Ca-DTPA (i.p.)	0.25	8	5 d, then twice a week		51	36	
		+	+	+					
		Pyran (i.v.)	(50 mg)	1	5 d				
	²³⁹ Pu nitrate (i.v.) (19% ultrafiltrable)	Ca-DTPA (i.p.)	0.25	8	5 d, then twice a week	33 d	69	89	
		Pyran (i.v.)	(50 mg)	1	5 d		104	94	
		Ca-DTPA (i.p.)	0.25	8	5 d, then twice a week		77	71	
		+	+	+					
		Pyran (i.v.)	(50 mg)	1	5 d				
		²³⁹ Pu nitrate (i.v.) (8% ultrafiltrable)	Ca-DTPA (i.p.)	0.25	11	5 d, then twice a week	49 d	57	92
	Ca-DTPA (i.p.)		0.25	11	5 d, then twice a week			60	
	+		+	+					
	Glucan (i.v.)		(60 mg)	3	5-7 d				
	Ca-DTPA (i.p.)		0.25	11	5 d, then twice a week			47	
+	+		+						
Pyran (i.v.)	(70 mg)	3	5-7 d						
Guilmette and Lindenbaum 1976 - Argonne									
Mouse	²³⁹ Pu nitrate (i.v.) (35% ultrafiltrable)	Ca-DTPA (i.p.)	0.25	6	5 d, then twice a week	24 d	67	54	
		Pyran (i.v.)	(50 mg)	1	5 d		93	94	
		Ca-DTPA (i.p.)	0.25	6	6 d, then twice a week		82	29	
		+	+	+					
	Pyran (i.v.)	(50 mg)	1	5 d					
	²³⁹ Pu nitrate (i.v.) (<0.3% ultrafiltrable)	Ca-DTPA (i.p.)	0.25	8	5 d, then twice a week	32 d	97	93	
		Ca-DTPA (i.p.)	0.25	8	5 d, then twice a week		289	66	
		+	+	+					
		Pyran (i.v.)	(50 mg)	1	5 d				

TABLE 19.12. Continued

Animal Species	Radionuclide (route of entry)	Chelate (route of entry)	Treatment			Period of Observation	TU Retention (% of control)	
			Dose per Treatment (mmol · kg ⁻¹)	No. of Treatments	Time after TU Injection		Skeleton	Liver
Gruner and Seidel 1976 - Karlsruhe								
Rat	²³⁹ Pu citrate (i.v.)	Zn-DTPA (s.c.)	0.3	4	2-5 d		79	20
		Triton (i.p.)	(750 mg)	1	2d		117	62
		Zn-DTPA (s.c.)	0.3	4	2-5 d	6 d	66	26
		+	+	+				
		Triton (i.p.)	(750 mg)	1	2 d			

UR = urethane

HQ = 8-hydroxyquinoline hydrochloride

Glucan = a yeast cell wall polysaccharide

Pyran = pyran copolymer, condensation product of divinyl ether and maleic anhydride

Triton = non-ionic detergent Triton WR 1339

Source: Modified from Volf 1978, Table XIII.

A scan of table 19.12 indicates some degree of enhancement of the effectiveness of DTPA in some cases. However, the effect is modest at best. It is more notable in liver than in bone, as might be expected from the much greater role of phagocytosis in the movement of entrapped radionuclides in the liver.

Not shown in the table is the fact that some of the additives (e.g., glucan) have significant toxicity by themselves. This led to searches for less toxic derivatives.

Other combination therapies were reviewed briefly in earlier sections, and many more will appear when we consider the nonchelator approaches. The ones considered in this section are a sample of those where there was overt attention to providing an adjunct to one of the main-line chelators.

b. Mixed-Ligand Therapy

Mixed-ligand therapy is similar to adjunctive therapy except that the two agents are expected to act by chelation rather than by mixed mechanisms described above for adjunctive therapy. We have already seen some examples in reviewing the earlier work on citrate. The most notable example, and the one usually meant by the term "mixed-ligand therapy," involves one of the few scientific scandals in the field of radioisotope toxicology.

In 1978, Schubert, who had by now shifted from the large research laboratories to a small liberal arts college in Holland, Michigan (Holland College), published a paper in *Nature* with a collaborator, S. K. Derr, on therapy with salicylic acid and Ca-EDTA in combinations (Schubert and Derr 1978). The combination was reported to remove virtually *all* of the plutonium burden from mice, including that deposited firmly in bone. This was hailed as a major breakthrough in chelation therapy. As detailed by Mays et al. (1981), nearly all of the world's laboratories working on chelation therapy for deposited radionuclides dropped everything to test the mixed-ligand hypothesis. This included Argonne, Battelle-Northwest, and the University of Utah in the United States; the Medical Research Council Radiobiology Unit and the National Radiological Protection Board in the United Kingdom; and the group at Karlsruhe in West Germany. The spectacular results could not be confirmed. The best that could be found

was a residual retention of about 30%, not much below that found in the best of the other chelation experiments. It was never 0% as claimed in the original paper.

In view of these conflicting findings, Schubert repeated the work and checked out the older data. To his dismay, he found that major portions of the data had apparently been invented by Derr! Schubert subsequently published notes retracting the original findings and giving the correct information. He also checked out catechol and tiron in combinations with DTPA and EDTA and found no significant difference from either compound alone (Schubert 1979, 1980).

As Mays points out, this episode probably cost the research organizations a half a million dollars, as well as delaying work in progress.^(a) It is especially unfortunate that it should have happened to Jack Schubert, who essentially initiated the idea of complex formation and pioneered the field along with Harry Foreman. He should be remembered for these contributions much more than for the mixed-ligand fiasco, in which he was not only blameless, but acted with responsibility and dispatch to clear the air.

E. Nonchelating Therapy

We are now ready to consider work done using means other than complexing or chelation to prevent deposition or to promote removal of radionuclides. This extends back to the work with radium done in the 1930s at MIT-MGH^(b) using diet, hormones, vitamin D, etc., to alter calcium metabolism. It includes a very miscellaneous collection of approaches. Since much of it has already been touched upon, and much of it is obvious, we will make no attempt at a complete review.

In contrast to the approaches to actinide therapy that received their major attention along with the development of the main-line chelators, much of the work using nonchelation methods relates to other radionuclide groups, especially those that, like strontium, behave like calcium in the body. Some of it applies to mobilization from the lung and will be considered in the section on therapy of inhaled radionuclides.

A very satisfying general review, which includes the agents and processes pertinent to this section, is the one by Bair and Smith (1969). They mention, among others, the following approaches to therapy:

1. decorporation by physical processes—e.g., whole-blood transfusions, use of an artificial kidney with an ion exchange column, surgical excision of contaminated wounds, pulmonary or peritoneal lavage, etc.
2. ionic dilution—e.g., addition of stable forms of the radioelement (i.e., isotope dilution), use of elements with closely related metabolic properties.
3. biological means for decorporation—e.g., alteration of physiological processes, either to mobilize the element, to stimulate recovery processes, or to prevent its deposition. This includes manipulation of diet.
4. radioprotective agents—e.g., cystamine and other radical scavengers to ameliorate the radiation effects (see the introduction to this chapter).

(a) It will be recalled that startling, but not necessarily dishonest claims, in the area of radiation standards, effects of fallout, etc., have cost the research community much larger sums. See chapters 12 and 16.

(b) See chapter 1 and section I A.

Among the examples of ionic dilution, the use of stable iodine to prevent uptake of radioiodine by the thyroid has already been discussed. Decreased retention of tritium by drinking large quantities of water with or without administration of a diuretic and use of Mg^{2+} for decreasing radiostrontium levels in bone are further examples.

For a review of the relatively early work, we turn to the ANL meeting in 1955. Animal work reviewed therein includes the following approaches in addition to the complexers and chelators already described:

		Rating(a)
For ^{239}Pu	Ti citrate (Rosenthal, Argonne)	+++
	Mn gluconate (Rosenthal, Argonne)	++
	Fe gluconate (Rosenthal, Argonne)	++
	Mg gluconate (Rosenthal, Argonne)	++
	Ca gluconate (Rosenthal, Argonne)	++
	Al citrate (Rosenthal, Argonne)	++
	Th citrate (Rosenthal, Argonne)	++
	Parathyroid extract (Copp, Berkeley)(b)	0
	Parathyroid extract (Arnold, Utah)	++
For ^{91}Y on skin	Mn gluconate (Rosenthal, Argonne)	+
	Fe gluconate (Rosenthal, Argonne)	+
	Ti citrate (Rosenthal, Argonne)	++
	Mg gluconate (Rosenthal, Argonne)	0
	Na salicylate (Rosenthal, Argonne)	?
	Parathyroid extract (Copp, Berkeley)(b)	0
For ^{89}Sr and ^{90}Sr	Stable Sr (MacDonald, UCLA)	+
	A series of 32 miscellaneous agents (MacDonald, UCLA)	see text
	Stable Ca (MacDonald, UCLA)	0
	High Ca diet for 2 months (Copp, Berkeley)(b)	+
	Low P diet (Ray, University of Washington)	+++
	Rachitogenic diet + ammonium chloride (Ray, University of Washington)	++
	Diuresis induced by different agents (MacDonald, UCLA)	0
	Detergent plus epinephrine on wounded skin (Copp, Berkeley)(b)	see text

Of all of these, only a few showed marked effects in terms of increased excretion, reduced retention in bone, or both. The ratings given by Marcia Rosenthal are indicated beside the items. The three-plus rating was the highest. Obviously, some fairly heroic procedures were quite effective but would be fraught with dangers in clinical use for humans.

Of the series of thirty-two chemical agents tried by MacDonald in 1950, all of them readily available, only a few definitely decreased skeletal accumulation of

(a) For removal from bone.

(b) Copp had moved to the University of British Columbia by the time of the meeting, but it is presumed that most of the work reported was done before he left Berkeley.

orally administered strontium (either radioactive or stable). These were in order of decreasing efficiency: magnesium sulfate, sodium sulfate, ammonium amidopolyphosphate, two carboxylic-type cation exchange resins, a colloidal phosphorylated glucoside, calcium phytate, pectin, bran cereal, castor oil, and a hydrophilic laxative derived from plantain (MacDonald 1956).

Some agents actually *increased* skeletal accumulation of ingested strontium. These were: powdered milk, tannic acid, inulin, sodium alginate, and a modified starch.

The work at the University of California, Los Angeles (UCLA), with ^{90}Sr - ^{90}Y differed in outcome somewhat from that using the much larger quantities of stable strontium. The researchers at UCLA were unable to alter "more than slightly" the percentage of radiostrontium dose retained. The gloomy outlook on radiostrontium removal in these early days is clearly revealed by the summary that MacDonald gave to his paper at the Argonne meeting. It is quoted below:

We must conclude that the status of the "medical armamentarium" for treatment of radiostrontium poisoning, as a physician might put it, is truly lamentable. In our opinion, there is some hope for reducing the danger from exposure to radiostrontium via ingestion or inhalation by the maintenance of a highly positive metabolic calcium balance, *before* exposure is anticipated. If, after an incident, it is learned that radiostrontium has been inadvertently swallowed, then oral treatment with Epsom salts or sodium sulfate, for example, within the first hour, should decrease its intestinal absorption. The value of ingesting milk products while the radiostrontium is still in the stomach or gut has not been demonstrated unequivocally as yet. However, immediate intravenous injection of *moderate* quantities of stable strontium or calcium gluconates and possibly the infusion of protein hydrolysates or pectin may be of some aid.

At present, we have no agent which will lower the radiostrontium bone burden significantly, if the isotope has been in the body for more than a few hours. (MacDonald 1956).

Full reporting is contained in the paper. This was primarily in the days before chelation therapy. We have already seen that the standard chelators did relatively little for strontium removal. However, research continued on other means, much of it in European laboratories. We will consider this now.

The excellent review by Nelson from the United Kingdom (Nelson 1963) gives details of additional work with strontium, mostly with the same substances as used earlier, but adding strontium lactate, calcium chloride, and sodium and calcium lactate. All had only marginal effects. However, the same was true of chelators. Nelson's review has an excellent summary of newer work on dietary modifications, including work done at the University of Tennessee-AEC Animal Farm at Oak Ridge (chapter 13) by Comar and associates, by Palmer and associates at Hanford, Clarke and associates at Hanford, and by Cohn and associates at NRD. In addition, Nelson considers work by Catsch and collaborators at Karlsruhe and studies in France.

The additional work could hardly be said to offer great hopes from the animal experiments toward application to strontium uptake or removal in humans. Little further work was done in the United States or the United Kingdom.

Ways to reduce absorption of ingested radiostrontium were included in the 1969 general review by Bair and Smith.

A moderately early set of experiments was carried out by Volf (1963) while he was still at the Institute of Radiation Hygiene in Prague. Attempts were made to reduce the absorption of radiostrontium from the gastrointestinal tract by

barium sulfate and normal calcium phosphate administered orally to rats and humans. Phosphates increased the fecal excretion of radiostrontium, but lowered urinary excretion so that total excretion remained the same. This bespeaks some reduction in gut absorption. Sulphates increased the amount of strontium in the small intestine at early times, but later promoted urinary excretion. There was a small influence of orally administered chlorides, but this, like the other substances, was most effective when the substances were given in "sufficient concentrations," and in this case, shortly before the radiostrontium injection.

At the Second European Congress on Radiation Protection of the International Radiation Protection Association, cited earlier, work was reported on mineral sorbents for reduction of absorption of radiostrontium and radiocesium from the intestinal tract of dogs and rats (Borisov et al. 1973, USSR), decorporation of strontium with sodium alginate and some radioprotective agents (Máté et al. 1973, Hungary), and another try at zirconium therapy for ^{85}Sr and ^{144}Ce (Severa 1973, Czechoslovakia).

In the first work, adsorbents used to delay or prevent ^{85}Sr absorption (polyantimonine, KU-Z resin, sodium alginate, BaSO_4 , and "Adsobar") showed high efficiency. Polyantimonine was the most efficient and was recommended for human use. In the same work, derivatives of ferrocyanides (Berlin blue, Prussian blue, cobalt ferrocyanide, nickel ferrocyanide, all in soluble form; and insoluble Berlin blue) were tried in the case of ^{137}Cs adsorption. Highest efficiencies (above 90%) were found for the ferrocyanides.

In the second work, the objective was again retardation of absorption of strontium. In addition to strontium, the animals were given x-irradiation. The radioprotectors seemed able to complex strontium and reduce retention. The irradiation increased retention. The sodium alginate reduced retention to about 50%, the largest change seen in retention as contrasted to absorption.

Work on zirconium used soluble zirconium compounds given orally or intravenously for possible retardation of the absorption of ^{85}Sr or ^{144}Ce from the gastrointestinal tract. The percentage of injected dose of ^{144}Ce in liver was reduced from about 71% to a low of about 52%, using zirconium nitrate given intravenously. Skeletal retention was very low, about 1.1%, but the same zirconium compound reduced it to 0.7% of dose. The zirconium had essentially no effect on retention of ^{85}Sr except for zirconium citrate in a form called ZrC given by mouth. If both the radioisotope and the complexer were given simultaneously, the percentage of ^{85}Sr in tibia was reduced from 1.6% of injected dose to about 0.6%. The authors conclude that all of the investigated chemicals had a significant effect in reducing ^{144}Ce in liver and femurs, but that the change in ^{85}Sr in bone was not biologically significant.

Another approach was that used by Richmond and Furchner (1961) for removal of ^{137}Cs . They used a diuretic, "DIOMOX," in rats and found the turnover rates of two of the components of the normal cesium retention equation were increased about 20%.

Relatively recent work from Belgium (Vanderborght, Van Puymbroeck, and Babakova 1978) studied the effects of alginate administered simultaneously by two routes on the distribution and excretion of strontium deposits of long standing. The philosophy was that earlier work had indicated that sodium alginate was somehow activated by incorporation into bread. This was based in turn upon the finding of a marked increase in the concentration of radioactive strontium in blood (mice) when alginate was added to a diet containing starch. There was also some work on an ambulant human volunteer. The regimen for the

animal experiment combined alginate administered intraperitoneally, and alginate in a starchy dough made part of the diet. The concentration of ^{85}Sr in blood of the mice rose by a factor of five. About half of the mobilized strontium appeared to be available for urinary excretion, practically none for increased fecal excretion. The amounts in liver, kidney, and spleen also increased. However, the portion in bone (femur) either increased slightly or remained the same. Thus, little benefit is to be expected from these processes once the strontium is within the tissues. They seem to move the strontium around a bit but not accomplish much net decrease of body or bone burden. So much for strontium and cesium removal by nonchelator means. Some work using nonchelation methods for removal of actinides was cited in the discussion of combination therapy above. Little more needs to be said here about actinide mobilization since the results were fairly uniformly uninteresting. However, there are still a few important radionuclides that were approached by nonchelation methods and some further combinations worthy of note.

At Los Alamos, Richmond, Drake, and London (1973) demonstrated effective removal of radiorubidium by ferric ferrocyanide without interference with sodium or potassium homeostasis.

Ruthenium exposures are of considerable practical importance. As reviewed earlier in this book (e.g., chapter 9), ruthenium releases from the Hanford production facilities stimulated experimental work not only on respiratory hazards, but on possible therapeutic removal. Much of this was done at Hanford and involved the inhalation route, which we will come to presently.

The chemistry of ruthenium is so complex that predictions of the effect of chelators were not certain. However, most of them turned out to be ineffective, probably because ruthenium forms very stable complexes with proteins. Catsch and Seidl (1963) screened a number of compounds and did find one that caused a pronounced reduction in retention of ^{106}Ru in tissues. This was a long chain sulfur compound called "BATE" (for 1:2-Bis-[2-di(carboxymethyl)aminoethylthio] ethane). This is a dithiol and could be viewed as a cross between BAL and the DTPA-type compounds. The ruthenium-BATE complex left the blood much more rapidly than ^{106}Ru alone. However, the reactions of ruthenium are slow, and large differences in mobilization were difficult to obtain.

Other nonchelator approaches for various elements are fairly obvious and have been tried in most of the laboratories engaged in work on therapy of incorporated radionuclides. One which is not obvious was mentioned by Bair and Smith (1969): administration of a substance that will change the pH of the stomach to a more alkaline value and thus reduce the solubilization of the radionuclide that normally occurs in the acid environment of the stomach.

With liver engaging almost as much attention as bone as a deposition site for plutonium, some interesting combination therapies have been tried. One (Rosenthal et al. 1973) used glucan, the polysaccharide derived from the cell walls of baker's yeast. It was postulated to foster disruption of intracellular aggregates of plutonium that characteristically form in liver. The work involved mice and trials of glucan alone, DTPA alone, and the two combined. Forty-seven days after administration, net removal of plutonium from the liver was 8.5% with glucan, 11.5% with DTPA, and 19.5% with combined therapy. The mobilization from liver was considered to be at least partly accomplished by intracellular penetration and action of the glucan, which brought the plutonium out where it could become available to the DTPA.

Some of this work involves trials on man without extensive testing on animals. We will review these in section V.

A considerable effort in animal experiments has been directed toward decontamination procedures for wounds and skin. These involve both chelation and nonchelation methods. Bair and Smith at PNL (1969) give an in-depth review of the processes involved in skin absorption, including a useful review of the anatomy and physiology of skin, the rate of penetration of many substances through skin, and the influence of injury by wounds or burns thereon. They give an interesting review of work by investigators at NRD (Loeffler and Herron 1951) in which it is shown that the vasoconstrictor, epinephrine, can markedly reduce the absorption of radiostrontium in rats. They also discuss French work using iontophoresis for removing radioelements from skin (Michon 1956) and ultrasonic methods for the same in work at Hanford (Neef and Ballou 1957).

The above potpourri of agents and methodologies is hardly amenable to summarization. It does demonstrate that few logical stones have been left unturned in the quest for therapy of deposited radionuclides. The animal work contributed many important pieces of information, both encouraging and discouraging. It formed the basis for decisions regarding therapeutic procedures to apply to man—many of which stood the test of clinical trial. A few routines have been established out of all of this. This culmination of the extensive and frequently discouraging animal work will be apparent in section V.

F. Therapy for Inhaled Radionuclides

The number of animal experiments on removal of radionuclides deposited in the body by inhalation is not in proportion to the importance of the inhalation route of intake. This may be because the large efforts toward decorporation of stable metals had already fixed upon other routes, or it may have been because of the technical difficulty of inhalation experiments with radioactive materials.

Major studies of therapeutic removal of inhaled radionuclides did take place at two of the U.S. laboratories deeply engaged in pulmonary radiotoxicology: Hanford's Pacific Northwest Laboratory in Richland, Washington, and the Lovelace Inhalation Toxicology Research Institute in Albuquerque, New Mexico. The work began first at Hanford and was quite general in scope. The work at Lovelace began considerably later (the laboratory was not in existence, of course, when the work began at Hanford). There was also good work in several European laboratories.

The Hanford efforts began in the 1950s, but the published reports began in the 1960s. Tombropoulos and Bair (1962) led off with a study of the removal of inhaled ^{144}Ce – ^{144}Pr from rats. They tried phenylephrine hydrochloride with or without DTPA, DTPA alone, and the detergent "Pluronic F68." There were two experiments, one terminated twenty-one days after exposure, the other fifteen days after exposure. Retention in liver and lung was very significantly reduced, particularly when treatment was started as soon as one hour after exposure. The DTPA appeared to be the prime agent. The investigators were greatly encouraged toward removal of other insoluble radionuclides from the lungs.

However, in the next year, the Hanford group (Tombropoulos, Bair, and Park 1963) had to report that neither DTPA nor "Pluronic" was very effective in removing $^{239}\text{PuO}_2$. Yet, the importance of removing plutonium and similar insoluble actinides stimulated hundreds of further trials both in the United States

and Europe. Work was reported in dogs a few years later (Tombropoulos, Bair, and Park 1969).

Results were summarized in the IAEA symposium, Diagnosis and Treatment of Radioactive Poisoning (see Bair, Tombropoulos, and Park 1963) and at the Hanford symposium, Inhaled Radioactive Particles and Gases, held in May 1964. At that meeting, Tombropoulos (1964) presented a review of the many therapeutic procedures (not only chelators) for removal of inhaled radionuclides applied in animal experiments. The bulk of the work had been done at Hanford, although researchers from a few other laboratories had contributed (e.g., Charles LaBelle who had moved fairly recently from Rochester to Jefferson Medical College in Philadelphia to work in the active pulmonary toxicology center headed by H. Brieger).

1. Physiological Approaches

Early approaches to therapeutic removal of radionuclides from the lungs were directed toward stimulation of lung clearance by stimulation of phagocytosis and of mucus-transport, application of bronchodilators, application of substances which reduce the tenacity and viscosity of pulmonary secretions (surfactants), and combinations of these.

Harking back to the phenomenon examined in chapter 9 that pulmonary clearance rate frequently increased when the deposited mass increased, LaBelle and Brieger (1960) and LaBelle, Bevilacqua, and Brieger (1964) tried adding "inert" agents to increase the mass deposited in lung, hoping thereby to increase clearance rates and thus sweep out some of the deposited radioactivity. They tried carbon, sand, asbestos, silica gel, and aluminum hydrate. The carbon (from India ink) had the greatest effect. The lung burden was reduced to 30% of the control using silver iodide (Ag^{131}I) as the radioactive material.

Unfortunately, workers in other laboratories, primarily Hanford, could not obtain such a large effect for other radionuclides, e.g., $^{144}\text{CeO}_2$, $^{59}\text{Fe}_2\text{O}_3$, $^{239}\text{PuO}_2$, and $^{106}\text{RuO}_2$. In fact, the lung burdens were sometimes increased. The work is described in the review by Bair and Smith; some of the data are shown in table 19.13, modified from Bair and Smith.

TABLE 19.13. Effect of Phagocytic Stimulating Agents on Removal of Radioactive Particles from the Lung

Radioactive Particle Inhaled	Test Agent	Method of Admin.	Duration of Test (days)	Lung Burden (% control)	References
Ag^{131}I *	Carbon (Peerless Mk17—channel black)	aerosol	1+	30	LaBelle, Bevilacqua, and Brieger (1964)
$^{144}\text{CeO}_2$ †	Carbon (India ink) > 1 mg deposited in lungs	aerosol	7	110	Bair and Hennacy (1962)
$^{59}\text{Fe}_2\text{O}_3$ †	Carbon (India ink) > 1 mg deposited in lungs	aerosol	21	110	Bair and Dilley (1966)
$^{239}\text{PuO}_2$ †	Globulin + pluronics F-68 + DTPA + hyaluronidase	aerosol	21	120	Tombropoulos, et al. (1964)
$^{106}\text{RuO}_2$ †	Choline	aerosol	7	110	Willard (1966)

* Given by intratracheal injection to rabbits.

† Inhaled by rats.

Source: Modified from Bair and Smith 1969. Reprinted with permission of Pergamon Press, Elmsford, New York, copyright 1969.

Note that the test agent included substances other than carbon, sometimes mixtures, and that the test agent was inhaled, as was the radionuclide, but not along with it.

An extensive cadre of parasympathetic drugs, mucolytic and surface active agents was tried for removal of ^{106}Ru , ^{144}Ce , ^{239}Pu , and ^{59}Fe . The results are shown in detail in the review by Bair and Smith, with the experimental work coming again primarily from Hanford. There was little consistent effect on lung clearance. Bronchodilators (e.g., phenylephrine HCl, Isuprel) showed slight effectiveness, mucolytic agents (Alevaire, Dornovac [desoxy ribonuclease] and Aerosol TR), and surface-active agents (Pluronic F-68, Triton, Tween-80) were essentially without effect except for an experiment on plutonium removal quoted below. Pulmonary irritants appeared to hasten removal of some insoluble oxides (e.g., $^{106}\text{RuO}_2$) from rats, but the results were inconsistent and difficult to substantiate. Also, the purposeful administration of pulmonary irritants to humans would require clearly life-threatening deposits of radioactivity and marked increases in clearance.

The results with expectorants (Terpin hydrate, sodium iodide, Isoprel plus ammonium chloride, Alevaire plus ammonium chloride) were likewise of marginal benefit or even made things worse.

Complicating all of this was the influence of the physical state of the inhaled agent as well as its chemical form. The only generalization that Tombropoulos could draw regarding physiological means for hastening removal from the lung was that agents that decreased mucus secretion showed some promise of expediting clearance, while agents that increased mucus secretion tended to increase retention. Apparently, the considerable reduction of Ag^{131}I burden in the lung by carbon particles shown in the work of LaBelle et al., the largest effect seen (table 19.13), was idiosyncratic.^(a)

It should be added that although most of the test administrations in the Hanford work utilized aerosols of the therapeutic agent, for reasons we will examine presently, use of intraperitoneal or other parenteral routes did not alter the picture appreciably.

The normal pulmonary clearance process is one of nature's most efficient mechanisms. It is not really surprising that we could not do much to improve upon it in normal subjects. Unfortunately, we do not have information for situations where clearance was not normal. The effect of these various physiological manipulations might be of more importance in the presence of the types of pulmonary pathology where clearance is abnormally slow. Thus, the above work is primarily applicable to healthy workers. It might or might not apply verbatim to general populations with their complement of emphysemics, etc. Future research might profitably be directed toward this facet.

2. Complexing Agents

Even while the physiological means were being investigated, chelating agents of the EDTA, DTPA type were added to some of the mixtures (see, for example, the work with $^{239}\text{PuO}_2$ in table 19.13). However, the enhancement factors for these mixtures were not promising.

(a) LaBelle introduced the radioactive material by intratracheal instillation rather than by inhalation. Since no work was done using inhaled Ag^{131}I , we cannot determine whether it was the technique that accounted for the difference.

Somewhat more encouraging results were seen in experiments of Schmidtke (1964) reported at the Hanford symposium, Inhaled Radioactive Particles and Gases. She tried having guinea pigs inhale a fog of a 25% DTPA solution and also gave daily subcutaneous injections for one week. This regimen produced a significant increase in clearance of ^{91}Y from the lungs and more rapid excretion in the urine. However, Hanford studies with inhaled plutonium, done well before the cited symposium (Tombropoulos, Bair, and Park 1963) indicated that neither DTPA nor TTHA had much effect on removal of this radionuclide from the lungs.

Further work turned to a variety of radionuclides, some of which is shown in table 19.14, modified from the review of Bair and Smith.

TABLE 19.14. Effect of Chelating Agents on Removal of Inhaled Radionuclides

Radionuclide Compound	Test Agent	Animal Species	Treatment Method	Duration of Test (days)	Lung Burden (% control)
$^{91}\text{YCl}_3$	DTPA	guinea pigs	aerosol immed. after exposure, subcut. daily	8	2
$^{91}\text{YCl}_3$	Hexameta-phosphate	mice	aerosol—9 treat. begin immed. after exposure	15	40*
$^{239}\text{PuO}_2$	DTPA + Pluronic F-68	rats	aerosol	29	120
$^{239}\text{Pu}(\text{NO}_3)_4$	Diethyldithio-carbamate	rats	subcutaneous injection	40	110
	TTHA			40	71
	DTPA			40	89
$^{106}\text{RuO}_2$	EDTA	rats	aerosol	14	120
	TTHA			14	130
	DTPA			14	120
$^{144}\text{CeO}_2$	DTPA	rats	aerosol—beginning 1 hr after exposure†	21	7
	DTPA		aerosol—beginning 24 hr after exposure	21	23
	DTPA		aerosol—beginning 1 hr after exposure	15	11
	DTPA		aerosol—beginning 24 hr after exposure	15	31

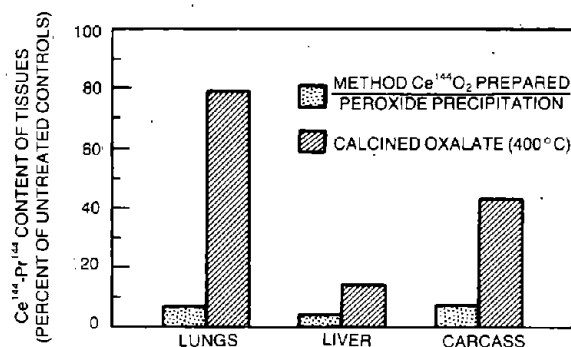
* Estimated from histograms in author's paper.

† I.P. administered DTPA was also effective.

Source: Modified from Bair and Smith 1969. Reprinted with permission of Pergamon Press, Elmsford, New York, copyright 1969.

All of the work quoted is from Hanford except the work with $^{91}\text{YCl}_3$, which was done by Schmidtke in Freiberg and Gensicke and Nitschke (1964) in Berlin. Obviously, plutonium and ruthenium were much more tenaciously held in lung than yttrium or cerium and were much more difficult to mobilize. If the cerium was calcined before inhalation, removal of it became more difficult. This is illustrated in figure 19.11. Thus, solubility of the inhaled material can be a controlling factor as would be expected.

FIGURE 19.11. Effect of DTPA treatment on removal of inhaled $^{144}\text{CeO}_2$ in rats. Rats were exposed daily for 30 min to aerosols produced from 25% DTPA and sacrificed after 3 wks. Data are means of 6-12 rats. (Redrawn from Tombropoulos and Bair, cited in Bair and Smith 1969. Reprinted with permission of Pergamon Press, Elmsford, New York, copyright 1969.)



Because of the importance of finding a good therapeutic regimen for inhaled insoluble^(a) plutonium, additional animal work was done, both at Hanford and at Lovelace. Schmidtke's work, in Europe, had already shown that chelators like DTPA were rapidly absorbed from the lung. Because of the convenience of self-administration from an atomizer, some of the work aimed at clinical uses of the therapeutic agents in the form of inhaled aerosols. In fact, the inhalation route did seem to confer some additional effectiveness to the therapeutic agent (Bair et al. 1973). It appeared that most of the increased removal came from lung and liver, little from deposits in bone.

Annual reports from the Hanford laboratories in the late 1950s, and those of its successor organizations, contain continuing references to work on the removal of inhaled plutonium as well as other actinides, particularly americium. It also extended to species other than rodents. While we laud this dogged persistence, there seems little need to detail the results, since there were no major improvements in the overall effectiveness of the *chelators alone*.

An illustration of the nuances of plutonium removal as seen in Hanford work is shown in figure 19.12A and B. Figure 19.12A shows that treatment of dogs with the detergent "Pluronic" yielded greater fecal and urinary excretion from deposits of $^{239}\text{PuO}_2$ than did DTPA. Figure 19.12B illustrates the rather miserable amount of reduction in body burden of inhaled plutonium in rats by a number of chelating agents.

Work at the Lovelace Foundation Inhalation Toxicology Research Institute (see chapter 9) concentrated largely on pulmonary lavage in combination with

(a) Soluble forms, of course, proceed to tissues such as bone or liver rather quickly, and removal can be approached by the methods described in earlier sections of this chapter.

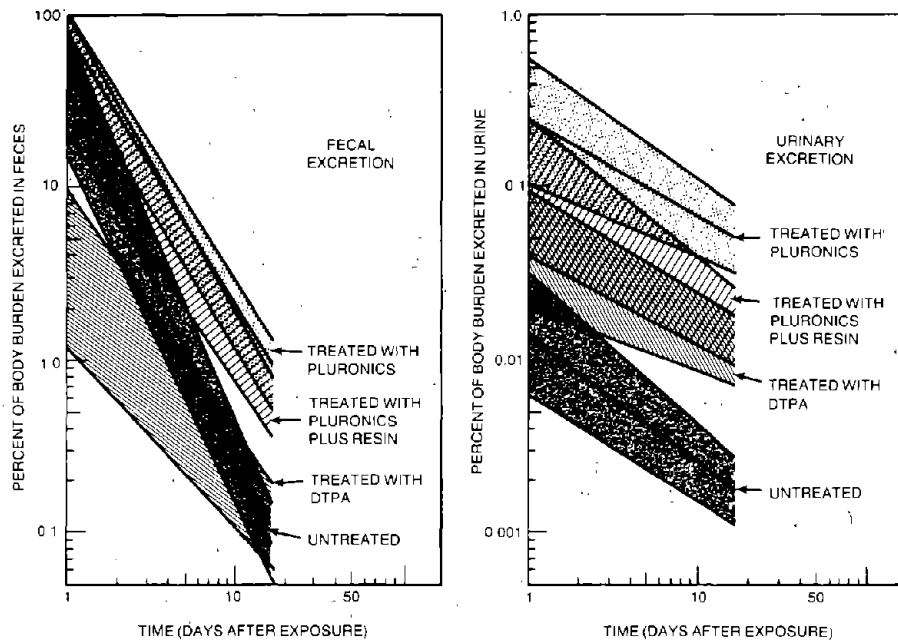


FIGURE 19.12A. Effect of Pluronic and DTPA on excretion of ^{239}Pu in dogs after inhalation of $^{239}\text{PuO}_2$. (Redrawn from Bair, Tombropoulos, and Park 1963.)

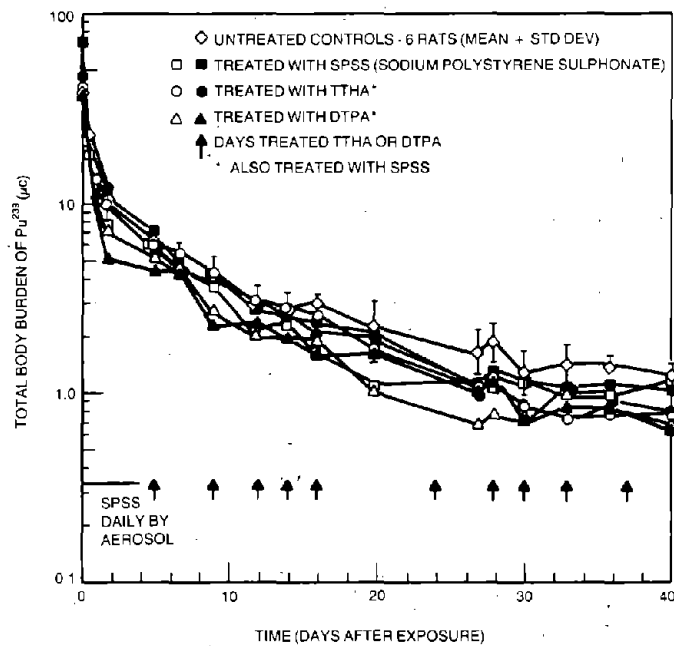


FIGURE 19.12B. Effects of DTPA, TTHA, and SPSS on removal of ^{239}Pu in rats after inhalation of plutonium nitrate. (Redrawn from Bair, Tombropoulos, and Park 1963.)

chelators (see next section), but they did some work with intravenously administered DTPA for the removal of inhaled materials (e.g., Pfeleger et al. 1972a,b). Very significant reductions were noted in the content of lung, liver, and skeleton after twenty-eight days when DTPA was given one hour after inhalation. As always, there was less effect if the DTPA was applied later, but even with a five-day delay, lung content was reduced by 50%. There was, however, little reduction of liver and skeletal burdens with the delayed treatment. Urinary excretion was likewise much less affected by the late treatment.

This work points up a fairly common way in which removal of inhaled radionuclides sometimes differs from that for other routes of entry. Some substances appear to become fixed in lung with almost the same speed as in bone. Other substances seem to go through a phase in which the deposit in lung is more mobile than deposits in tissues like skeleton. Thus, while speed of attack for therapy is mandatory for some substances, e.g., plutonium, others give more chances for useful mobilization from lung. This has an important corollary. Many investigators have been concerned that uncritical application of chelation therapy might move substances from lung to a less accessible site such as bone instead of allowing the lung's natural clearance processes to operate to their maximum initially.

An interestingly different approach was tried by other investigators at Lovelace (Thomas, Scott, and Thomas 1969; Thomas and Chiffelle 1974). Zymosan, obtained from yeast, was known to stimulate reticuloendothelial cell proliferation. It was reasoned that such stimulation of reticuloendothelial system function in the lung might hasten phagocytic removal of particulate material. There were changes in several respiratory parameters, but an increase in net clearance of ^{137}Cs in fused clay did not occur. The work gave more information on clearance kinetics and mechanisms than therapeutic promise.

3. Lung Lavage

The procedure of washing out deposits of unwanted material from the lungs, while hardly commonplace, has become firmly established in the medical management of pulmonary obstructive diseases. Application of pulmonary lavage to the removal of radionuclides occurred in several laboratories, primarily around potential clinical needs. In 1968 and 1969, Sanders, at Hanford, demonstrated removal of $^{239}\text{PuO}_2$ particles by lavage of excised rat lungs (Sanders and Adey 1968, Sanders 1969). This was quickly followed by work with living animals at Lovelace (Pfeleger, Wilson, and McClellan 1969; Pfeleger et al. 1969). In this work, ^{137}Cs in fused aluminosilicate was used. Work with lavage also began in laboratories in Europe, particularly France.

Since pulmonary lavage is hardly an everyday happening, a short review of the procedure seems in order. The one used for beagles, and closely similar to that used for man, is described carefully by Muggenburg, Felicetti, and Silbaugh (1977). It is excerpted below:

Briefly, the procedure was to anesthetize the patient with a mixture of halothane, nitrous oxide and oxygen and place a Carlen's double lumen bronchosprometry tube in the trachea to provide functional separation of the right and left lungs. Using the anaesthetic gas mixture, nitrogen was washed out of the lungs and the airway tube to the lung to be lavaged was clamped. While ventilation was maintained in the other lung, isotonic saline was slowly introduced into the lung until a volume equal to the functional residual capacity of that lung was reached.

Additional volumes, approximately tidal volumes, were then added and drained repeatedly. Finally, all the fluid was drained and ventilation was reestablished.

Another lavage procedure has also been used experimentally in beagle dogs to remove inhaled radioactive particles and to treat chronic obstructive lung disease in children. In this procedure, a single lumen endotracheal tube was placed in the trachea after induction of anaesthesia. The patient was placed in a position so that the lung to be lavaged was down [i.e., in the down side, so that fluid would travel into it]. After placement of the endotracheal tube, the patient was hyperventilated to lower arterial carbon dioxide tension to induce a state of temporary apnea. During apnea, isotonic saline was introduced into the lung by gravity. The volume of fluid used approximated the total lung capacity for the lavaged lung. The fluid was then drained and the cycle of hyperventilation, introduction of fluid and drainage of the fluid was repeated until completion of the desired number of washes. (Muggenburg, Felicetti, and Silbaugh 1977, references omitted)

Experimental procedures used in small rodents range from variations of the above to surgical removal of the lavaged lung and draining of the contents into a suitable receptacle for counting.

The Lovelace group extended their work to baboons and to one human who accidentally inhaled ^{239}Pu (see section V).

From initial success with relatively mobile $^{137}\text{CsO}_2$ to less mobile ^{137}Cs in fused aluminosilicate, they extended to ^{95}Zr - ^{95}Nb , $^{144}\text{CeCl}_3$, ^{144}Ce in fused aluminosilicate, ^{238}Pu and ^{239}Pu oxide particles, and ^{241}Am oxide particles. Lavage was equally effective in removing these particles from the lung. However, multiple lavages were needed (the Lovelace group used ten) to attain really significant removals, e.g., 40% to 44% of the initial lung burden. Furthermore, it was found that lavage was not very effective for material of short retention time. Indeed, it appeared that it might be better to leave such deposits alone, for the lavage procedure can interfere with normal clearance processes and is not needed anyway for short half-life materials. On the other hand, for some of the more tenaciously held substances, lavage seemed to be the only effective removal method available.

Illustrative of the results at Lovelace and of special interest because it involves the use of "real world" aerosols of mixed oxides is the information shown in table 19.15. The removal from lung is striking. Changes in excreta and in other tissues are not so striking and are sometimes in the wrong direction, though not significantly so.

Lavage with a DTPA solution in contrast to lavage with saline increased the effectiveness; at least for the removal of ^{144}Ce . (Pfleger et al. 1972a,b; Muggenburg et al. 1972) and probably for the other radionuclides tried.

An important feature of the experimental work with lung lavage was the finding that the time of initiation of treatment was not critical up to several months after exposure. The incremental efficiency of lavage seems to fall off with time when a series is given at relatively short intervals, e.g., two days. By contrast, a sometimes surprisingly large new increment can be mobilized when lavage is resumed after a considerable period without treatment.

Much attention was devoted in the Lovelace work to the hazards of lavage. It is not a totally innocuous procedure, as we will see in section VI. However, on the basis of the fairly extensive animal experience, a recommended procedure for humans was worked out. Careful evaluation is needed in each individual case.

Somewhat surprisingly, and in some contradiction to the precautions emphasized above, the French have reported ability to lavage *both* lungs at the same

TABLE 19.15. Plutonium Activity in the Feces, Urine, Lavage Fluid and Tissues of Beagle Dogs^(a) Exposed by Inhalation to Industrially Produced Mixed Oxides of Plutonium and Uranium and Subsequently Treated with Lung Lavage and DTPA.^(b)

Aerosol	Number of Dogs	Mean Initial Lung Burden (μ Ci)	Percent Initial Lung Burden						
			Feces	Urine	Lavage Fluid	Lung	TBLN	Liver	Skeleton
Controls									
PuO ₂ , UO ₂	2	1.7	16	0.2	—	79	0.6	0.1	0.2
(Pu,U)O ₂	2	1.5	22	0.3	—	70	0.3	0.2	1.6
²³⁹ PuO ₂	2	3.9	24	0.1	—	70	0.4	0.01	ND
Treated									
PuO ₂ , UO ₂	3	0.68	14	0.4	57	21	0.4	0.01	3.2
(Pu,U)O ₂	2	11	6	0.3	56	34	1.6	0.1	0.1
²³⁹ PuO ₂	3	1.0	15	0.3	66	13	0.9	0.04	0.4

(a) Over 64-day period.

(b) Treatment consisted of ten lung lavages and eighteen intravenous injections of DTPA.

Source: Modified from Muggenburg et al. 1979.

sitting, in baboons at least (Nolibé et al. 1977). All U.S. practices have employed only one lung at a time and even then with a two-day interval between treatments. Thus, any given lung received lavage at intervals of no less than four days. One reason for the urgency felt by the French workers was their finding that ²³⁹PuO₂ produced early lung pathology in baboons at lung burdens a factor of three lower than in dogs or rodents (Metivier et al. 1974). If applicable to humans, obviously the technique could accomplish more rapid removal, but it requires very careful standardization with provisions for individual variations as described in detail by Nolibé et al. (1977). The decision to use bilateral lavage would presumably rest upon the demonstrated presence of truly dangerous quantities of a dangerous radionuclide. This statement is made despite the conclusion of the French workers that the main medical risk of lavage is associated with repeated anesthesia of the subject.

A modicum of work has been done to prove reduction of biological effects of inhaled radionuclides by virtue of lavage procedures. The Lovelace group contributed most to U.S. work on this facet (Boecker et al. 1974; Muggenburg and Mauderly 1975; Silbaugh et al. 1975). The work summarized in the 1977 review by Muggenburg used dogs exposed to aerosols of ¹⁴⁴Ce in fused aluminosilicate particles. They studied the survival time, incidence, and severity of radiation pneumonitis, and any other relatively early pathological changes. There was no doubt about the effectiveness of the treatment in terms of early effects, i.e., less pneumonitis, longer survival. The French work already cited included studies of pathology, but it was directed more toward effects of the lavage treatment than effects of the deposited radionuclide. They did show significant increases in the survival time of the treated animals.

We will now review experience, both experimental and clinical, in humans and close with a review of the pharmacology and toxicology of the main-line chelators.

V. Experience in Man

Experience concerning the therapeutic removal of radionuclides from the human body has been gained both as part of experimental investigations at the tracer level and as a result of clinical situations resulting from accidental intakes. Frequently, the information on therapy was part of more general studies of the metabolism of radionuclides in man. We will review this experimental work first.

A. Experimental Studies

The bulk of this type of work in the United States was done in the laboratories and metabolism ward of Dr. Herta Spencer and her many colleagues at the U.S. Veterans Administration Hospital in Hines, Illinois. Initial work was done at the Montefiore Hospital in New York, where Dr. Spencer was a collaborator (and wife) to Dr. Daniel Laszlo in the Division of Neoplastic Diseases until his death in June 1958. A few years later, she moved to the Hines facility and has made a full career of these studies. There were occasional collaborators from other organizations, e.g., the AEC's Health and Safety Laboratory in New York. Except for needed technical and nursing assistance, this work represents largely the efforts of the principal investigator. It required the facilities of a major metabolism ward and the large professional and technical staff always associated with these operations.^(a)

The work concentrated mostly on strontium, since a convenient short half-life isotope was available (^{85}Sr), and the work began in the midst of the agitation to gain all possible knowledge about the principal radionuclides in fallout (chapter 13).

The first report of broad scope came at the Argonne symposium, Therapy of Radioelement Poisoning, held in 1955. Laszlo and Spencer (1956) gave an overview of effects of Na-EDTA and Ca-EDTA on urinary calcium excretion, including radiocalcium; distribution of lanthanum when injected as the chloride or in chelate form (versenate); influence of EDTA on urinary excretion of the lanthanum-140-EDTA complex (marked increase); and the effect of calcium level on urinary excretion and plasma levels of ^{85}Sr . The findings presaged those to be taken up presently. All work involved patients, but their clinical conditions were quite disparate.

At the second Atoms for Peace Conference in Geneva, Switzerland, Laszlo and Spencer (1959) presented a summary paper on radiostrontium metabolism and decontamination in man. The work was done at the Montefiore Hospital, and it references a long series of detailed individual publications beginning in the 1950s.

(a) Some of the patients were essentially volunteers whose presence in the hospital was adventitious to the study, others were patients with advanced neoplastic disease, especially with bone metastases, as described in the many publications. In all cases, the radionuclide doses were strictly at the tracer level.

Calcium intake and variations in the calcium status of the body were found to have effects on the metabolism of strontium in man just as in animals and as they had earlier been found for radium (chapter 1). Absorption of ingested tracer strontium remained in the same range whether the calcium intake was high or low. However, it appeared that any situation that enhanced calcium excretion also enhanced strontium excretion. Indeed, there was somewhat greater enhancement of the strontium loss. Addition of ammonium chloride to produce acidosis caused enhancement of urinary ^{85}Sr excretion, but it was not as large as that caused by calcium gluconate. The two treatments together caused a further enhancement, which was roughly additive. Calculated body burdens of ^{85}Sr were clearly reduced. Of special interest was the fact that oral administration of ammonium chloride was effective in removing radiostrontium as late as fifteen days after exposure. This interaction of calcium and strontium led to a study of twenty adults who received simultaneously tracer levels of ^{85}Sr and ^{45}Ca , given orally. More calcium was absorbed, more absorbed radiostrontium was excreted via the kidney. (For more on this discrimination between calcium and strontium see chapter 13.)

Laszlo and Spencer (1956) also give data on ^{85}Sr content of bone with and without metastases (osteolytic metastases) from some of the patients who were in advanced stages of neoplastic disease. Also the effects of sodium-EDTA were reported in this summary. They were just as negative in this work in man as the animal work had predicted.

The strontium work in man was further described by Spencer and Laszlo (1960) in the book on metal binding edited by Seven and Johnson. The report reiterated the substance of the Geneva paper but gives more information on the clinical state of the patients and its possible influence on strontium excretion. Most of the studies were carried out with low calcium diets. Both urinary calcium and urinary strontium were lowest on a low calcium diet. They were higher on a high calcium diet and highest on a high calcium diet plus ammonium chloride. In this work, Na_2EDTA decreased urinary ^{85}Sr excretion. There was a compensatory increase in excretion after cessation of the chelator treatment.

At the 1962 IAEA symposium, which we have already quoted in many other connections, Spencer has a further review of the removal of radiostrontium from man (Spencer 1963).^(a) There was expansion of the routes and mixes of calcium gluconate and ammonium chloride; addition of the more effective chelator, Ca-BAETA , which we met in the review of the animal experiments; and the influence of stable strontium was compared to stable calcium. The newer chelator, BAETA, was indeed more effective as presaged by the animal experiments. Stable strontium appeared to be more effective than stable calcium in producing a carrier effect. Work published in 1965 in collaboration with investigators from the New York Health and Safety Laboratories of AEC (Spencer et al. 1965) further extended these findings.

In still later work, Spencer and her colleagues included agents that might influence the gut absorption of strontium. In 1968 a news release from the National Center for Radiological Health of the U.S. Public Health Service (HEW-T-4, dated 26 January 1968) espoused the use of aluminum phosphate gel to

(a) This and all subsequent work came from the Hines Veterans Administration Hospital.

inhibit gastrointestinal absorption of strontium. This was based on work done at Hines. It was published in the *International Journal of Applied Radiation and Isotopes* and in *Radiation Research*. It is summarized in what appears to be the last major paper on strontium in man from this group, viz., in the AEC-sponsored symposium on Biomedical Implications of Radiostrontium Exposure, held at Davis, California, in 1971 (Spencer, Kramer, and Samachson 1972). The added isotope was ^{85}Sr as before. The intestinal absorption was calculated from fecal excretion and also from the blood plasma level. In addition, technology had advanced to the point where the ^{90}Sr in the diet, urine, and feces could be determined by low-level beta counting without addition of any exogenous isotope. This may be important if the form of the element in food or body fluids is a complex different from that present at early times or is in some other way altered so that solubility might be changed. These studies with ^{90}Sr were complete balance studies.

There was confirmation and expansion of the earlier work on diet, ammonium chloride with and without chelators, plus gastrointestinal absorption work using vitamin D, lactose, lysine, parathyroid extract (no effect with any of these),^(a) and aluminum phosphate gel (marked decrease in ^{85}Sr absorption). Diuretics were variable in action. Those that did increase urinary excretion of strontium accomplished no net gain since there was a compensatory inhibition of excretion later. Intravenous stable strontium and magnesium had small but definite effects toward increasing excretion. The newer chelating agent BAETA proved the most effective of all the measures taken.

On balance, this laboratory work on man demonstrated that "something could be done" about strontium uptake and removal even though it was not comparable to the more dramatic results (in a relative sense) with plutonium and other actinides. The procedures are hardly simple, nor do they remove large quantities of deposited strontium. The efforts to decrease gastrointestinal uptake that looked promising did not immediately become part of the recommended routine clinical management practices. However, the message seems to have gotten across, for recent (NCRP 1980) summaries of recommended actions include administration of aluminum phosphate immediately in cases of strontium contamination.

Spencer's laboratory was engaged in very broad studies of the metabolism of metals in man. She did not by any measure limit her efforts to strontium. The rare earth elements came in for extensive experimental work (Rosoff et al. 1961; Spencer and Rosoff 1963). Lanthanum, yttrium, and scandium (^{140}La , ^{90}Y , and ^{46}Sc) were administered intravenously in either ionic or chelated form.^(b) Urinary excretion was low for the ionic forms, almost quantitatively complete in twenty-four hours for chelates. Gut absorption of the ionic forms was almost zero. Blood studies showed binding to various globulin fractions by lanthanum and scandium, but no binding at all by yttrium. The chelating agents of the EDTA-DTPA type were quite effective in removal of tracer doses of rare earths, with DTPA the more effective. There was a relationship between urinary

(a) While parathyroid extract did not materially affect absorption, the status of the thyroid and parathyroid glands did have a marked influence.

(b) Some of the earliest work was presented by Laszlo at the Oak Ridge symposium on the rare earths discussed in chapter 4. It did not concern removal techniques, just the basic metabolic behavior.

excretion (of yttrium in this case) and the stability constant of the chelates with yttrium, much as we saw in the animal work.

Tissue distribution data in man are given in these reports, but there is no indication of how the measurements were made. Since they are expressed as percentage of dose per unit wet weight of tissue, it is presumed that there were either autopsy results or collections from surgical excisions. As expected from the animal work, these rare earth elements were sequestered in components of the reticuloendothelial system to a large degree. This may help account for their relatively ready availability for removal by chelators. Very significant removals were possible.

In a study devoted to scandium alone (Spencer and Rosoff 1965) and another to ^{65}Zn in man (Spencer and Rosoff 1966), relatively easy removal by standard and special chelating agents (zinc study) was demonstrated.

These successes led the Hines group to a degree of optimism concerning potential means for removing many of the fission products from the human body in the event of contamination. The work on therapy in toto plus many detailed experiments on the way in which man handles a variety of radionuclides of importance to contamination by fallout or other means reflects a laudable determination and constancy of purpose on the part of the principal investigator and unusual continuity of financial support from organizations that undoubtedly had many other demands on their resources.^(a)

There has been nothing else in U.S. laboratories comparable to Herta Spencer's series. However, there have been a few more or less isolated studies with volunteers. One concerned the behavior of promethium, a prominent component of radioactive waste. The work was done at Hanford by Palmer and Nelson (1970).

The isotope of concern is ^{147}Pm , but this is a very low-energy beta emitter which cannot be determined in humans except by measuring amounts excreted. Palmer and Nelson decided to harden up the excretion model for promethium by use of ^{143}Pm , which has a half-life of about 13.5 days and beta energy compatible with the use of whole-body counting techniques. Six volunteers were injected with $0.1 \mu\text{Ci}$ of $^{243}\text{PmCl}_3$, and metabolic parameters were studied for one year. DTPA was studied in eight volunteers. A marked effect of time after injection of the radionuclide appeared. Removal went from 90%, to 25%, to 5% with administrations at thirty minutes, twenty-four hours, and eighty days after the injection, respectively. This applied to urinary excretion. Fecal excretion was more or less constant with time and independent of the time interval between ^{143}Pm and DTPA administration.

There have been a few investigations using volunteers or adventitious patients in European laboratories. These focused mainly on the basic metabolic behavior of the radionuclides in man and did not engage so much in work on therapeutic removal. There are, however, a few exceptions, as described below.

Volf, while he was still at Prague, carried out studies on radiostrontium decorporation in several cancer patients (Volf 1963). This was part of a study built around animal experiments and two inhalation accidents. He studied the effect of orally administered barium sulfate on the turnover of administered radiostrontium (^{85}Sr). Urinary excretion of ingested strontium decreased several-fold following barium sulfate treatment, while there was an increase in the

(a) A large number of individual papers giving detailed results could not be referenced herein. They can be found in the bibliographies of the review-type papers cited.

amount in feces. Volf concluded that the effect of the barium was to reduce absorption of strontium from the gastrointestinal tract.

There was also considerable interest in European laboratories and some in the United States in the use in man of alginates, jelly-like substances obtained from sea kelp, as mentioned briefly in consideration of the animal experiments. Alginates effectively reduce gut absorption of many radionuclides. Experimental work by the U.S. Public Health Service (Stara and Waldron-Edward 1968) showed considerable promise for this agent in cats. However, these compounds tend to have high viscosity, tend to be difficult to ingest, and are not very readily available in the United States. For this reason, clinical protocols for the United States indicate a preference for aluminum phosphates, but European practice has continued to emphasize alginates for prevention of strontium absorption.

The metabolic data from these several experiments with man indicate that more strontium is handled in urine and excreted via the kidneys in man than is the case with most laboratory animals, an important generalization.

Some of the European work on Prussian blue included studies on man. (There was animal work on both sides of the Atlantic.) This substance (potassium ferri ferrocyanide) has been found effective in removing cesium, thallium, and rubidium, at least.

An example, using cesium, is seen in work from Karlsruhe and Norsk Hydro's Institute of Cancer Research by Madshus et al. (1966). Two of the authors took 1 μ Ci of carrier-free ^{137}Cs and initiated treatment with Prussian blue ten months later. The biological half-time was reduced from about 110 to 115 days to about 40 days. Parallel animal work showed little dependence upon treatment schedule. Since Prussian blue is not recognized in the U.S. Pharmacopoeia, nor approved by the Food and Drug Administration, any use for therapy in humans in the United States must be considered as a special emergency measure.

Further detail on this and many other drugs outside of the mainstream of the research we are reviewing can be found in the enormously useful report from the U.S. National Council on Radiation Protection and Measurements (NCRP) entitled *Management of Persons Accidentally Contaminated with Radionuclides* (NCRP 1980).^(a)

Because of the lack of suitable isotopes in the actinide series for conducting safe experimental work at the tracer level, there has been essentially no experimental work in humans with these elements, except for studies around body burdens received occupationally, idiopathically, or in nonoccupational accidents.

The general agreement between the results of animal work and the experiments with normal humans outlined in this section is much greater than might be expected.

(a) The Scientific Committee preparing this report reads like a partial "Who's Who" of American workers in the field of radionuclide therapy: George L. Voelz, Los Alamos, Chairman; H. David Bruner, formerly USAEC and DOE, Bonita Springs, Florida; Victor H. Smith, Hanford; Herta Spencer, Hines V.A. Hospital; Niel Wald, Pittsburgh; John W. Healy, Los Alamos (consultant). By the time of this activity, Harry Foreman, Bill Bair, and Jack Schubert had gone on to other things and were not automatically included as they would have been if the report had been prepared earlier. "Dag" Norwood, Hanford, had retired, or he would have been included also.

B. Accidental Exposures—Clinical Management

1. Overview

This book concerns research and the results of research. Many excellent compendia exist on the handling of radiation accidents. The nuances of clinical management will not be expanded upon here (see, for example, the recent report of the NCRP [1980] and the earlier review by Foreman [1963]). Our purpose is to examine the ways in which the extensive research findings can and have been applied to unplanned intakes of radionuclides by humans and the extent to which these clinical experiences confirm, refute, or extend the basic research findings.^(a)

Before considering specifics, the reader is reminded again that the subject of this section is but a specialized part of an important area of clinical toxicology and research on the role of metals in biomedical phenomena. We will bypass many more or less commonplace sources of potential exposure and therapy thereof (e.g., lead and mercury) since these have been considered extensively in other connections. Also, the use of sodium iodide to block uptake of radioiodine (see NCRP 1977; *Federal Register* 1978; Eisenbud 1973; and earlier chapters) requires no further exposition here.

Accidental contamination of humans with radionuclides is far from commonplace, especially if the number of potential opportunities for exposure is considered. The potential damage is serious enough, however, that every major installation handling amounts of radioactivity above certain prescribed amounts has a room set aside for possible decontamination procedures and personnel available or on call with at least rudimentary training in the applicable techniques. This frequently includes local police and fire personnel. The most informative cases from the scientific standpoint have occurred where well-trained physicians with research interests in the subject and associated laboratory facilities and personnel were either on hand or brought into the case. The industrial medical department of every major nuclear installation has for many years had chelating agents ready for possible emergency use.

The report of the NCRP, already cited, covers the subject of management of contaminated persons in considerable depth and should be consulted for specific guidance. The table of contents^(b) is reproduced below for the assistance of the reader:

- Preface
- 1. Introduction
- 2. Quick Reference Information
- 3. Initial Management of the Patient
 - 3.1 Introduction
 - 3.2 Uptake and Clearance Mechanisms
 - 3.3 The Contaminating Radionuclide
 - 3.4 Initial Radioactivity Measurement
 - 3.5 On-Site Management
 - 3.6 Transportation

(a) We are purposely omitting discussion of the clinical uses of chelating agents for other purposes (see, for example, Seven and Johnson 1960; Holland, Danielson, Sahagian-Edwards 1953).

(b) Modified from NCRP 1980; section 2 is of special interest to the medical practitioner.

- 3.7 Hospital Management
- 3.8 Evaluation of the Contaminated Patient
- 3.9 Public Health Considerations
- 4. Diagnostic Techniques to Measure Radioactive Contamination
 - 4.1 Surface Contamination Measurements
 - 4.2 Penetrating (External) Radiation Measurements
 - 4.3 Measurements by Excretion (Bioassay) Sampling
 - 4.4 In Vivo Measurements
- 5. Conceptual Basis for Treatment Decisions
 - 5.1 Timeliness of Data
 - 5.2 Risk/Benefit Considerations
 - 5.3 Soluble Versus Insoluble Compounds
 - 5.4 Multiple Isotope Effects
- 6. Resume of Experience With Important Radionuclides
 - 6.1 Americium
 - 6.2 Californium
 - 6.3 Cerium
 - 6.4 Cesium
 - 6.5 Cobalt
 - 6.6 Curium
 - 6.7 Gold
 - 6.8 Iodine
 - 6.9 Mercury
 - 6.10 Phosphorus
 - 6.11 Plutonium
 - 6.12 Polonium
 - 6.13 Radium
 - 6.14 Strontium
 - 6.15 Technetium
 - 6.16 Thorium
 - 6.17 Tritium (Hydrogen-3)
 - 6.18 Uranium
- 7. Therapy Procedures and Drugs
 - 7.1 Skin Decontamination
 - 7.2 Treatment of Contaminated Wounds
 - 7.3 Treatment of Internal Contamination
 - 7.4 Lung Lavage

APPENDIX A—Radiological Assistance Plan (RAP)

APPENDIX B—Definitions

References

(NCRP 1980)

The treatise on treatment of incorporated transuranic elements by Volf (1978) lists fifty-four separate incidents^(a) of actinide contamination that came to treatment with chelating agents. These extended from 1963 to 1973 and concerned only plutonium and americium, with two instances involving curium (see table on pages 1661 through 1664). At about the same time, Dolphin (1976) reviewed DTPA and its use in sixteen cases of therapy in humans for plutonium contamination in the United Kingdom and the United States. In both instances, there are many more cases of contamination via wounds than by inhalation or ingestion. In 1964, Piltingsrud reported that the Rocky Flats Plant near Denver, Colorado, operated by Dow Chemical Company and a prime handler of

(a) The numbering refers to incidents not cases. In some incidents, there were several cases and more than one publication on treatment.

plutonium, as we saw in earlier chapters, had had 1,159 wounds in the period since June 1957. About 30% of these were positive for contamination, albeit mostly at low levels.^(a) A summary of Hanford experience with plutonium over the period 1946 to 1967, with an update to 1971, is given by H. M. Parker (1973). It is shown in modified form as table 19.16.

TABLE 19.16. Summary of Hanford Experience With Plutonium

	From 1946 To 1967	Updated To 1971
Injury cases potentially contaminated	230	310
Cases containing measurable plutonium	136	162
Cases surgically decontaminated	86	100
Deposition above 5% MPBB	15	16
Deposition above 50% MPBB	5	5
Plutonium inhalation cases	1140	1501
Chelating agent used	12	13
Deposition above 5% MPBB	98	101
Deposition above 50% MPBB	12	14

Note: MPBB = Maximum Permissible Body Burden.

Source: Modified from Parker 1973. Reprinted with permission of Springer-Verlag, New York, copyright 1973.

This can be compared with the summary from earlier days shown in table 19.3. Note that inhalation cases greatly exceed injury cases (i.e., wounds) in the experience at Hanford. Also, the relatively few cases treated with a chelating agent can be taken as a measure of the portion considered potentially serious enough to warrant decorporation therapy.

Summaries of contamination incidents by radionuclides other than the actinides are not easy to come by. The furor over the toxicity of the actinides has eclipsed the fact that human cases include a considerable cadre of radionuclides. Many of them have already been discussed earlier in this book. An informative overview can be found in the NCRP report already cited. This includes a short statement regarding the relative incidence of cases for each of the radionuclides shown in the table of contents (see above). These include, incidentally, cases of overexposure caused by misadministration in medical use of some of the radionuclides, as well as the more conventional avenues.

(a) These numbers may seem high. However, anyone who has spent appreciable periods in the chemistry laboratory has more than likely been wounded more than once by glass tubing or other equipment. Add to this the need for awkward manipulations within dry boxes, the fact that the solutions being used were frequently very "hot," and it is not surprising that even a tiny pinprick becomes a contaminated wound. Sometimes the person is not even aware of having sustained a pinprick wound.

Despite the preponderance of cases where entrance has been by wounds, the greatest concern has focused on inhalation and, to a lesser extent, on ingestion cases.

We will now review some of the major instances that attracted attention or led to clear advances in knowledge.

2. Specifics

This section makes no attempt at complete coverage for the reasons given above.

a. Zirconium

The urgency to have some means of therapy at hand led the Hanford group and those responsible for medical care at the U.K. installation at Windscale to prepare stocks of zirconium citrate solutions for possible clinical use. This was based entirely upon the animal work sparked by Schubert and the lack of toxic effects seen therein.

It was natural for Hanford to be the first in the U.S. since they had the greatest potential for exposure to radionuclides. W. D. ("Dag") Norwood reported on their early cases in 1955. There were three trials of zirconium in man (Norwood 1956).

The first was a small dose administered to an incurable patient to test toxicity; none was noted. The second and third were employees with small fractions of the allowable body burden of plutonium attained by inhalation and ingestion in the first case, by a small break in the skin in the second. Both received repeated doses of 600 mg of zirconium in citrate intravenously. The preparation was made according to the formula developed by Schubert and contained both zirconium and sodium citrate. The results indicated some effect, but only from the very early doses. Indeed, it appeared that little could be gained by a series of zirconium injections, an idea reiterated by Schubert.

Norwood could detect no untoward effects of the zirconium. However, he was concerned about the effects of the accompanying sodium citrate and concluded: "These studies would indicate that the sodium citrate is the limiting factor and not the zirconium in the intravenous administration of zirconium citrate." (Norwood 1956, p. 37)

At the Windscale Works of the United Kingdom Atomic Energy Authority, two cases of plutonium contamination were treated with zirconium (Graham 1956). The first involved ingested plutonium, the second a pinprick wound. Perhaps because of the well-understood problems of administering the needed quantities of citrate, the U.K. investigators used zirconium malate. In the first case, two courses were given, about 350 mg over twenty-six days and about 400 mg spread over eight weeks beginning six weeks after the first course. The effects on excretion of plutonium were not clearly discernible, due partly to the large variability in urinalysis results. In the second case, zirconium malate was given in a series of five 50-mg injections. Effects on excretion were not commented upon.

In these cases, a totally unexpected side-effect of the treatment became apparent, viz., vertigo associated with vestibulitis. As usual, no connection was made between the treatments and the patient's symptoms for a considerable period.

Let Dr. Graham tell the story as taken from his extemporaneous remarks at the symposium.

Regarding Case 1:

At the beginning this patient seemed quite well. He complained of an unpleasant metallic taste during and for an hour or two after each injection. On some occasions he felt a little nauseated and had to rest for a few minutes after the injection.

After the 5th injection, however, he had an attack of vomiting and he went off work for a few days. His own doctor treated him for a mild febrile illness with gastric upset. He was taken suddenly ill again 17 days later and this time was hospitalized in the Medical Department. He complained of nausea, headache, giddiness and general weakness. He looked pale and collapsed at first but soon responded to bed rest, excess fluids and glucose, sedation and an alkaline mixture. While under treatment he had a moderate intermittent fever.

At this time no one connected his illness with zirconium. It was known that he had suffered from "bilious attacks" in the past, also he had been invalided from the R.A.F. on account of nervous dyspepsia. When he had recovered from his sickness he went away on leave for a few days but during this time he vomited copiously on four occasions. Despite this it was decided to give further zirconium in the belief that mobilization of plutonium was more important in the long run than these attacks of "gastritis" and "biliousness."

As time went on his symptoms became distinctly more definable as true vertigo. It was by coincidence that a second case (described below) had meantime found his way to an aural surgeon who diagnosed labyrinthitis. It then became clear that the first case also had labyrinthitis.

Vestibulograms taken by the aural surgeon showed almost complete suppression of labyrinthine function on both sides and confirmed the striking similarity between case (1) and (2).

(Graham 1956)

Regarding Case 2:

This patient also complained of a metallic taste which led to a distaste for food on many occasions, culminating in an actual loss of taste which was sufficient to cause some distress. There were headaches too, often severe, but here again one was misled because he suffered also from sinusitis and a deflected nasal septum.

A sharp attack of vertigo occurred two days after the 5th injection and from then on vertiginous bouts were frequent and distressing. Vomiting was not a feature although he was often nauseated and lost his appetite.

In due course he went to hospital for resection of his nasal septum and the attention of the aural surgeon was drawn to the vertigo. It was then that a diagnosis of toxic labyrinthitis was made, thus providing an important clue to the truth about Case 1, as has been described.

The labyrinthitis was bilateral and loss of function became virtually complete. Avomine was given to control the vertigo. As time went on the tendency to vertigo attacks disappeared and a year later all seemed normal. The taste sense also returned within a few weeks. The headaches however had persisted and were migrainous in character. It was difficult to say whether now, three years afterwards, there is much connection between the zirconium and the headaches.

(Graham 1956)

Following this there was much scrambling to find an explanation. Some proposed it was because the zirconium malate solution had been autoclaved and some degradation products had been formed; others that it was coincidence. Mice were given very large doses of zirconium malate, some batches of it thought to have been sterilized,^(a) without any signs of abnormal labyrinth

(a) Dr. Graham was not fully certain of this point, and this author has not found any further work or discussion of the subject.

function. To a degree, it has remained unresolved, but the conservative conclusion was that man reacts differently from most of the test animals to these moderately large doses of zirconium salts, at least the malate.

These toxic effects essentially ended the clinical trials of zirconium, although it was sometimes added to EDTA-type chelators (Dobson 1956).

b. Early Trials in Man with EDTA-DTPA

Again some of the earliest work was at Hanford. "Dag" Norwood and the medical department put EDTA at the ready for possible clinical use, even while the laboratory work was incomplete. They proposed very small doses and ultraconservative approaches, but nevertheless felt that the need to prevent bone deposition of elements like plutonium warranted some degree of aggressiveness.

The first case described by Norwood (1956) was one from Los Alamos, handled jointly by Norwood and Harry Foreman. This was a deposition of seven-years standing, presumably from inhalation of spray or vapor. The EDTA was given by slow intravenous drip, a method applied regularly in the early cases because too rapid administration of the chelator seemed to produce kidney damage in animals (see section VI). A total dose of about 5 g increased urinary plutonium excretion about tenfold.

More details were given in a paper by Norwood et al. at the Atoms for Peace Conference (1959). The first accident at the Hanford Atomic Products Operation that led to a body burden above limits (during more than thirteen years of operation) was an inhalation exposure due to a defect in a copper supply line. Treatment was instituted on the third day after exposure. It lasted seven months and involved 142 1-g doses of Ca-EDTA.^(a) Of these, 71 days involved intravenous doses and 21 days oral doses. There was complete collection of all urine passed.

Total plutonium excretion in urine was about 0.037 μCi from a body burden estimated at 0.36 μCi initially. Of the total excreted in urine, 0.033 μCi was passed during the Ca-EDTA treatments. About 0.35 μCi appeared in the feces. It cannot be said that these results indicated accelerated removal from lung, but it can be postulated that some plutonium leaving lung was shunted into excretion in lieu of deposition in bone.

By the time of the Hanford symposium on the biology of the transuranic elements in 1962, Norwood (1962b) could report on treatment of five Hanford employees who had carried variable amounts of plutonium for variable periods of time. The principal finding was that DTPA (they had turned to it instead of EDTA because of greater effectiveness) was fully as effective for decorporation therapy in humans as in animals. Oral DTPA^(b) was only about one-tenth as effective as that intravenously administered in increasing urinary output of plutonium, but it was about equal in hastening fecal output.

An early joint report from Los Alamos and Hanford (Foreman, Fuqua, and Norwood 1954) gave an opportunity to describe some early Los Alamos cases treated with chelators. The first was a wound caused by breaking of a flask containing $\text{Pu}(\text{NO}_3)_4$ solution. There was surgical removal of some of the contamination and early administration of Ca-EDTA. The results are shown in

(a) One gram was a convenient dose size since this was what the commercial ampules contained.

(b) The cumbersome method of slow intravenous drip was still in operation for the intravenous doses, and patient resistance led to many trials with the oral route.

figure 19.13, taken from Foreman's discussion of the cases at the Argonne symposium in 1955 (Foreman 1956).

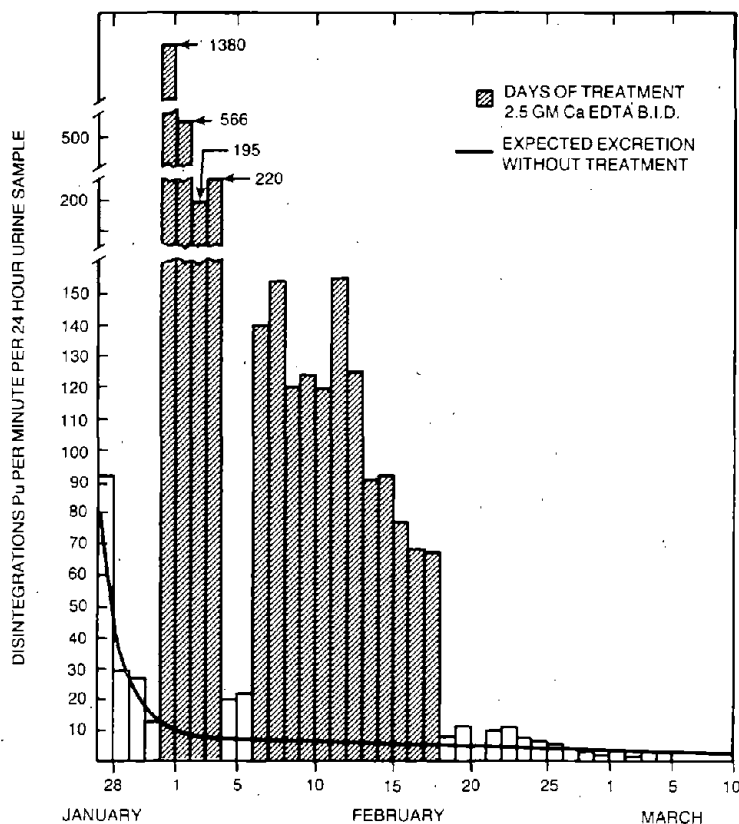


FIGURE 19.13. Urine excretion assay for Pu from wound case showing effect of Ca-EDTA. (Redrawn from Foreman 1956.)

Case 2 was an inhalation exposure. The increases in urinary excretion, while measurable after Ca-EDTA, were not nearly as spectacular, partly because treatment was delayed, and partly, it was thought, because exposure was by inhalation.

Another case involved ^{241}Am , ^{242}Am , ^{242}Cm in a "hot" mixture that exploded just before the ampule was to be opened, spraying the operator (an Air Force major) with the contents. After measures to remove as much activity as possible from the skin using EDTA washes, intravenous EDTA was started. Urinary excretion was rapid during periods of therapy, much slower during "rest periods." The latter were brought on by the patient's balking at the long-continued intravenous administrations. It may have been serendipitous, for the investigators were surprised to find unexpectedly large increments in excretion on resumption of therapy, a phenomenon that repeated itself several times.

Another early American case occurred at Berkeley and was described by Dobson (1956). A graduate student working with ^{241}Am at a level of 10^{10} dpm in

a glove box struck his left hand against sharp broken glass and "suffered a small puncture wound between the thumb and forefinger." Since preliminary evaluation failed to rule out a potentially serious medical problem, intravenous Ca-EDTA therapy was instituted. This began only one and one-half hours after the wounds were received. Urinary excretion was about a factor of ten higher during the periods with EDTA. Meanwhile, much was done toward wound decontamination and removal of seriously contaminated tissues by surgery. After seventeen days, treatment was interrupted because of evidence of incipient kidney damage, and the urinary excretion fell by a factor of about ten. A short period on zirconium citrate produced no observable change in ^{241}Am excretion.

Since the whole-body counter had just been put into operation at Argonne, it was considered appropriate to check the patient's body burden of americium using its 60-kV gamma rays. Marinelli made the measurements and calculated a body burden that agreed quite well with that calculated from the urinary excretion and amounts removed surgically. Dobson calculated that the EDTA therapy had reduced body retention by five- to tenfold.

French experience in the earlier days is described by Lafuma (1963). This concerns a wound contaminated with ^{239}Pu . DTPA was found to be extremely effective.

So much for early experience with plutonium and other actinides. There was much less with other radionuclides. The Hanford group had some experience with ruthenium, but not much can be said about clinical decorporation. Also, isolated remarks on other nuclides appear in discussion sessions at the several symposia cited and in annual reports, but we will have to bypass these. There are, however, some experiences in man with alkaline earths and other radionuclides that are of interest.

Of particular interest to the decade of the 1950s is the work done with the Marshallese exposed to fallout from a weapons test. (Details are in chapter 12.) Stanton H. Cohn describes the early attempts to alter the rate of removal of mixed fission products in this small population in a classic paper given at the IAEA scientific meeting in 1962 already cited (Cohn 1963). Additions were made in a personal interview with the author in September 1982 (Cohn 1982).

Cohn was at NRDL at the time of the work, although the published report came from Brookhaven, and the interview was there. As part of a mysterious and urgent message he received to prepare for a journey to the South Pacific were instructions to bring along all necessary materials for decorporation therapy. No hint was given as to what was to be decorporated! The fact that this request was made indicates again the urgency felt by all responsible for medical care of contamination incidents to "do something."

Cohn's report gives details of the exposure (chapter 12), including supplementary information obtained from pigs that happened to live on Rongelap. It concentrates on attempts to estimate the body burden of the exposed population by measurements of urinary excretion and other means. At fifty-two days after the event, an attempt was made to increase urinary excretion of the deposited fission products in seven Marshallese subjects^(a) using daily administrations

(a) One may wonder in view of the urgent request to take along materials for decorporation why the attempt was delayed fifty-two days. The most likely explanation is the time required to establish body burdens and to make decisions on who should be treated. Also, the magnitude of the contaminations were not as large as first expected.

of Ca-EDTA. The dose, administered orally, was 1 g per each twenty-five pounds of body weight. Urine was collected daily for five days. Mean gross beta activity, the only measurement possible under these field conditions, was about two and one-half times the pretreatment level. It was speculated, based on the animal experiments, that this represented largely rare-earth elements. No information was obtainable on possible amounts in individual tissues until the later work with whole-body and other external counting techniques (chapter 12). No reason is given for the relatively short period of therapy.

Japanese investigators reported simultaneously on the clinical status and treatment of the twenty-three fishermen exposed to the same fallout on the ship *Fukuryu Maru No. 5*. (Kumatori and Miyoshi 1963). Only two received decorporation therapy, viz., Ca-EDTA by intravenous injections over intervals of "about three months and seven months after the detonation." No increase of radioactivity in urine occurred.

Before we leave these early experiences, we should look briefly at a thorium incident that occurred at Argonne in the early 1950s (Hathaway et al. 1956). It involved ^{227}Th , which has a half-life of 18.2 days. A tiny puncture wound occurred through the glove in a glove box with contamination at 60,000 to 80,000 dpm. More to be on the safe side than because of conviction that dangerous amounts of activity were present, Ca-EDTA was administered. In contrast to expectations from animal experiments on thorium compounds, the EDTA was reported to have caused increased excretion. However, the rises are not nearly so large as with many other radionuclides. Marinelli commented that the form of the thorium (chloride) may have contributed to its mobility and that the ^{223}Ra daughter was preferentially removed from the wound.

These early clinical trials with chelators of the EDTA-DTPA type showed clearly that the basic predictions of the animal experiments could be applied to humans. They also failed to show significant untoward effects, with one exception, and that marginal. It must be emphasized, however, that the treatment periods were not really long by the standards of later work. Further, the work showed that split doses, even with significant rest periods between doses, did not unduly reduce effectiveness and could contribute greatly to the patient's acceptance of the therapy. In fact, doses after a rest period were surprisingly effective. Also, such pauses may have helped to prevent cumulative toxicity of the agents, as we will discuss in the next section. An exception to the above is the importance of rapid initiation of treatment to ensure that there be a good chance that chelation could prevent tissue deposition, particularly bone deposition. It will be noted that none of these studies included opportunities to study tissue retentions, except where whole-body counting was applied; and this was relatively rare in the early years.

3. Crescendo of Experience

The fifty-four cases summarized by Volf (1978), although they cover only plutonium, americium, and curium, give a reasonable overview of experience to 1976. His table is reproduced in modified form as table 19.17.(a).

Particular attention should be focused on the column giving the excretory multiplication factor. Factors from zero to as high as three hundred are evident.

(a) Since most of the references have already been cited in this book or will be discussed presently, only the name and installation are cited in this modified table.

TABLE 19.17. Decorporation of Plutonium, Americium, and Curium in Man. [Author, date, and location in bold.]

Case(s) No.	Compound	Radionuclide		Chelate (Route of Adminis- tration)	Dose per Treat- ment (g)	Total Number of Treat- ments	Total Dose (g)	Time After Contami- nation	Estimated Effect on Radionuclide Absorbed Fraction	
		Sus- pected Mode of Entry	Estimated Local Deposit (nCi) Initial Late						Excretory Multiplication Factor	Body Burden Reduction
Foreman, Fuqua, and Norwood 1954, Foreman 1963 - Los Alamos										
1	²³⁹ Pu nitrate	Wound		EDTA i.v. inf.	2.5	32 (2X daily)	80	5-8, 11-22 d	Urine: 100X	
2	²³⁹ Pu	Inhalation		EDTA i.v. inf.	0.1-2.5	~8 (2X daily)	16.1	7 a	Urine: 5X	
3	²⁴¹ , ²⁴³ Am ²⁴² Cm	Inhalation		EDTA i.v. inf.	2.0	16 (2X daily)	32	1-5, 8, 27, 28 d	Urine: >20X	Am, 10X
4	²³⁹ Pu nitrate etc.	Wound		EDTA i.v. inf.	2.5	12 (2X daily)	30	1h-4d, 16, 17 d	Urine: slow rise only	
Remarks: Diagnostic value (residual i.m. deposit)										
Dobson 1956 - Berkeley										
5	²⁴¹ Am	Wound		EDTA i.v. int.	1.0	47 (4X daily)	47	0-18, 21-31, 33-45, 50-60 d	Urine: 2-10X	
				+ Zr ci- trate i.v.	0.3	2	0.6	75 d	Zr: no effect	
Remarks: Limited excision										
Graham 1956 - Windscale										
6	²³⁹ Pu	Ingestion		Zr malate i.v. inj.	0.05	15	0.75	early-127 d	No effect	
Remarks: Toxic labyrinthitis										
7	²³⁹ Pu	Wound		Zr malate i.v. inj.	0.05	5	0.25	0-8d	No effect	
Norwood 1956 - Richland										
8	²³⁹ Pu	Inhalation, Ingestion		Zr citrate i.v. inj.	0.6	2-4	1.2- 2.4	0-5 d (6, 7 d)	Urine: 3X	
Remarks: 2 cases										
Norwood 1960a,b - Richland										
9	²³⁹ Pu nitrate	—		EDTA i.v. DTPA i.v. DTPA oral	0.1- 2.0 0.5-1.0	1-18 2 1-5	up to 14 up to 5,	3 h-8 a	Urine: DTPA 10-12X EDTA DTPA i.v. 12X oral	
Remarks: 6 cases										
Norwood 1962a - Richland										
10	²³⁹ Pu	Inhalation	400	DTPA i.v.	1.0	~25	~25	5-7 a	Urine: 8-55X	
Remarks: Drop of eff. with time										
Norwood 1963; Swanberg and Henle 1964 - Richland										
11	²³⁹ Pu nitrate	Wound	860	0.2 DTPA i.v. inf.	1.0-3.0	20	28	9 h-6 d, 50-54, 79-83, 99-103 d	Urine: 55-70X faeces: 50X	
Remarks: Sustained effect										
Baumgartner et al. 1965; Larson et al. 1968 - Richland										
12	²³⁹ Pu metal	Wound	36,000	200 DTPA i.v. inj. i.v. inj. flushing	1.0	~70	83	1 d-20 weeks 30-50 weeks	Urine: 5-30X flush: 40 nCi	
Remarks: 4 excisions										
Heid and Jech 1969 - Richland										
13	²³⁹ Pu air- borne	Inhalation	25	DTPA i.v. inj.		7	~7	0-21 d	Urine: ~10-500X	
Remarks: Case 2										
Jech, Anderson, and Heid 1972 - Richland										
14	²³⁹ Pu nitrate	Wound	1000	0.7 DTPA i.v. inj.		~20	~20	10 h-6 d, ~60-105 d	Urine: ~100X	~60%
Remarks: Case 2 sustained effect										

TABLE 19.17. Continued

Case(s) No.	Compound	Radionuclide		Estimated Local Deposit (nCi)		Chelating Treatment				Estimated Effect on Radionuclide Absorbed Fraction	
		Sus- pected Mode of Entry	Initial	Late	Chelate (Route of Adminis- tration)	Dose per Treat- ment (g)	Total Number of Treat- ments	Total Dose (g)	Time After Contami- nation	Excretory Multiplication Factor	Body Burden Reduction
Jech, Anderson, and Heid 1972 - Richland											
15	²³⁹ Pu nitrate	Wound	122	3	DTPA i.v. inj.	1.0	~60	60	2-91, 126-180 d	Urine: ~80X	~60%
Remarks: Case 3 sustained effect											
16	²³⁹ Pu nitrate	Wound			DTPA i.v. inj.		~13	~13	~6-60 d	Urine: 80-100X	50%
Remarks: Case 4											
17	²³⁹ Pu oxide	Inhalation			DTPA i.v. inj. inhal.		~8	~8	~2 h-21 d	Urine: ~2-3X	<10%
Remarks: Case 7											
Hammond 1959; Lagerquist and Hammond 1965; Boss and Mann 1967 - Rocky Flats											
18	²³⁹ Pu sol + insol.	Wound + inhalation	181	37	EDTA i.v. DTPA i.v. inj.	1.0-4.0 1.0	32 12		4.5 h-30 d 262-272 d 7a	No dose effect Urine: 15X	~2%
Remarks: Employee 1297 (exposed 1957)											
19	²³⁹ Pu sol + insol.	Wound (facial)	194	31	EDTA i.v. DTPA i.v. inf.	1.0-4.0 1.0	32 24		4.5 h-30 d 269-279 d 7a	No dose effect Urine: 10X	~15%
Remarks: Employee 2817											
Remarks: Exposed 1957											
Putzier et al. 1965 - Rocky Flats											
20	²³⁹ Pu	Wound	144,000	600	DTPA i.v. inf.	1.0	85	75	1 h - 18 months	Urine: 8000 nCi excess Eff. depends on dose and schedule	
Remarks: 4 excisions											
Lagerquist, Putzier, and Piltingsrud 1967; Boss and Mann 1967 - Rocky Flats											
					oral i.m. inf.	1.0-5.0 0.3	53 1	249 0.3	(also 2X daily)	Urine: up to 10X Urine: ~10X	
Remarks: Small local effect											
Lagerquist et al. 1965; Lagerquist, Allen, and Holman 1967; Lagerquist and Hammond 1965 - Rocky Flats											
21	²³⁹ Pu nitrate	Acid burns	310		DTPA i.v. inf.	1.0	11	11	1 h-17 d (also 2X daily)	Eff. very good	
Remarks: Employee 2302											
22	²³⁹ Pu oxide	Wound	113	19-37		1.0	10	10	1 h-18 d	Eff. incon- clusive	Removal of blood Pu
Lagerquist, Allen, and Holman 1967 - Rocky Flats											
23	²³⁹ Pu nitrate	Acid burns	300		DTPA i.v. inf.	1.0	27	27	1 h-27 d	Urine: two excretion half-lives	~97%
Remarks: Employee 3890 skin rash											
Hammond, Lagerquist, and Mann 1968 - Rocky Flats											
24	²³⁹ Pu - ²⁴¹ Am oxides	Inhalation	up to 270		DTPA i.v. inj.	1.0	4-5	4-5	1-5d	Urine: Pu/Am low eff. varying	
Remarks: 8 cases											
Lagerquist, Hammond, and Hylton 1972 - Rocky Flats											
25	²³⁹ Pu	Wounds	1160	19	DTPA i.v.		2-4	~2-4	~1-7 d	Urine: ~2 nCi excess	
Remarks: Pu burden verified post mortem											
Schofield 1969 - Windscale											
26	²³⁹ Pu oxide	Wound	1000	90	DTPA i.v. inj.	0.1-0.25	4	0.55	11 h-4 d	Little, if any effect	
27	²³⁹ Pu nitrate	Wound	1000	2	DTPA i.v. inj./inf.	0.25-1.0	8	3.9	0.5 h-14 d	Urine: 30-40X	

TABLE 19.17. Continued

Case(s) No.	Compound	Radionuclide		Estimated Local Deposit (nCi) Initial	Late	Chelating Treatment				Estimated Effect on Radionuclide Absorbed Fraction		
		Sus- pected Mode of Entry				Chelate (Route of Adminis- tration)	Dose per Treat- ment (g)	Total Number of Treat- ments	Total Dose (g)	Time After Contami- nation	Excretory Multiplication Factor	Body Burden Reduction
Schofield and Lynn 1973 - Windscale												
28	²³⁹ Pu metal	Wound	~5000	2		DTPA i.v. inj./inf.	0.25-1.0	10	4.3	2 h-14 d	Urine: ~20X	29%
Remarks: Case 5												
Hesp and Ledgerwood 1971; Schofield and Lynn 1973 - Windscale												
29	²³⁹ Pu nitrate/ oxide	Wound	800	150		DTPA i.v.	0.25-1.0	4	0.55	1-3 d	No effect	
Remarks: Case 6												
30	²³⁹ Pu nitrate/ oxide	Inhalation	≤12			DTPA i.v. inj.	0.25	?		Extended therapy	No effect	
Remarks: Cases 1-3												
31	²³⁹ Pu nitrate	Inhalation	110			DTPA i.v.	0.25-1.0	3	2.25	4, 29, 50 d		10-15%
Remarks: Case 4 sustained effect												
Howells et al. 1973; Schofield et al. 1974; Dolphin 1976 - Windscale												
32	²³⁹ Pu oxalate	Wound	14,200	≤1500		DTPA i.v. inj./inf.	0.25-1.0	41	12.7	40 min - 16 d, 70-99, 126-135, 159-163 d	Urine: ~0.6 nCi excess	28%
Caldwell 1967; Caldwell 1972; Brodsky et al. 1968 - Pittsburgh												
33	²³⁹ Pu- ²⁴¹ Am oxide	Inhalation	400	2		DTPA i.v.	1.0	3		5-7 d	Little, if any effect	
Remarks: External contamination												
Wald et al. 1968 - Pittsburg												
34	²³⁹ Pu, ²⁴¹ Am acid solution	Wound + inhalation	2000	200		DTPA i.v.	1.0	21	21	0-60, 70-130 d	Not evaluated	
Brodsky et al. 1969; Fasiska et al. 1971 - Pittsburgh												
35	²⁴¹ Am oxides	Inhalation	1800	400		DTPA i.v. inj./inf.	0.5-1.0	>125	>110	~1000 - 1800 d	Urine: 5-8X eff. dose- dependent	
Remarks: No side effect												
Brodsky et al. 1972 - Pittsburgh												
36	²³⁹ Pu- ²⁴¹ Am	Wound (hand amputation)				DTPA perfu- sion i.v. inj.	1.0	1	1	8 h	Not evaluated	
Remarks: Hand reattached + reamputated												
Sanders 1961 - Savannah River Plant												
37	²³⁹ Pu nitrate	Wound				Zr citrate i.v. inf.	1.2	1	1.2	2.5 h	No effect	
						EDTA i.v. inf.	1.0	15	15	3 h-6 d, 131-135 d (also 2X daily)	No effect	
Remarks: Abdominal pain and thirst on 5-6 d												
Jolly et al. 1972 - Savannah River Plant												
38	²³⁹ Pu nitrate	Wound	900	1		DTPA i.v. inf. inhal	1.0	~80	80	1-82, 312-943 d	Urine: 35X eff. depends on time and schedule	
Remarks: 2 excisions												
						EDTA p.o.	0.3	40	12	22-31 d (4X daily)	Eff. inconclusive	
Sanders 1974 - Savannah River Plant												
39	²⁴⁴ Cm relat. sol	Inhalation	14			DTPA inhal	1.0	8	8	2.5 h-40 d	No effect	
40	²⁴¹ Am, ²⁴⁴ Cm oxides		~450			DTPA i.v. inj. inhal.	1.0	15	15	0.50-101 d	Urine: 6X	

TABLE 19.17. Continued

Case(s) No.	Radionuclide				Chelating Treatment				Estimated Effect on Radionuclide Absorbed Fraction		
	Compound	Sus- pected Mode of Entry	Estimated Local Deposit (nCi) Initial	Late	Chelate (Route of Adminis- tration)	Dose per Treat- ment (g)	Total Number of Treat- ments	Total Dose (g)	Time After Contami- nation	Excretory Multiplication Factor	Body Burden Reduction
Lafuma 1963 - Fontenay-aux-Roses											
41	²³⁹ Pu nitrate	Wound	60,000	2200	DTPA i.v. inf.	1.0	~21	21	1-7, 28-32, 62-65, 80-84 d	Urine: 30-300X	
Remarks: 2 excisions											
Jeanmaire and Ballada 1971 - Fontenay-aux-Roses											
42	²⁴¹ Am soluble	Inhalation	180-300		DTPA inhal	—	7-8		6 h-50 d	No effect	
Remarks: 2 cases											
Plotnikova and Bajsogolov 1964 - Moscow											
43	²³⁹ Pu var. compounds				DTPA i.v. inj.	1.0-2.0	42	49	(2-7, 16-21 weeks)	Urine + faeces 60X	
44	²³⁹ Pu var. compounds				DTPA i.v. inj.	0.5-1.0	26	14.5	(3-15 d)	Urine + faeces 80X	
Remarks: Treatment schedule only; time after incorp. not indicated											
45	²³⁹ Pu var. compounds				DTPA i.v. inj.	0.25-0.5	26	7.25	(3-15 d)	Urine + faeces 80X	
Anderson et al 1970 - Mound Laboratory											
46	²³⁸ Pu insoluble	Inhalation	91-134		DTPA i.v. inf.	1.0	30-32	~30	1-16(I), 32-37(II), ~90, 135 d(III)	No effect(I); urine: ~2X(II); urine: 6-50X(III)	
Remarks: 3 cases, Pluronic ineffective											
Alderhout and Hunzinger 1971 - Eurochemie-Mol											
47	²³⁹ Pu nitrate	Inhalation	~7		DTPA i.v. inj. inhal.	0.5-1.0	4	2.5	16, 183, 298, 572 d	Urine: 10-100X	
Remarks: Sustained DTPA eff.											
Alderhout 1972 - Eurochemie-Mol											
48	²³⁹ Pu nitrate	Inhalation	3		DTPA i.v. inj. inhal.	0.5	2	1	298, 572 d	Urine: 10-50X	
McClellan et al. 1972a - Albuquerque											
49	²³⁹ Pu relat. sol.	Inhalation	450		DTPA i.v. (+ saline lavage)	1.0	12	12	8-20 d	Urine: 71 nCi lavage; 59 nCi	
Remarks: First lung lavage in man											
Ohlenschläger 1971 - Albuquerque											
50	²⁴¹ Am perchlorate	Wound	244	0.7	DTPA i.v. inj. + flushing	0.5	2	1	1, 12 d	Urine, faeces: ~6X flush, no effect	
Ohlenschläger and Schieferdecker 1973, 1976; Ohlenschläger 1976 - Karlsruhe											
51	²³⁹ Pu nitrate	Wound	200	1	DTPA i.v. inf. inhal.	1.0-2.0	6	9	1-11, 83 d, 375 d	Urine, faeces: 40-60% 50-100X (early)	
Remarks: Wound secretion											
					Zn-DTPA i.v. inf.	1.0	1	1	785 d		2.5% (late)
Testa and Delle Site - 1973 - Rome											
52	²³⁹ Pu oxide	Wound	70	0.2	DTPA i.v.	1.0	1	1	1.5 h	Eff. improbable	
Whalen and Davies 1972 - New York											
53	²⁴¹ Am oxide	Inhalation (ingestion)	?	70	DTPA i.v.	~1.0	>4	>4	12 a	—	2-4%
Remarks: Adult											
Cohen et al. 1976 - New York											
54			?	20	DTPA i.v.	~1.0	>4	>4	12 a	Urine: ~8X faeces: ~1/5 urine	37%
Remarks: Adolescent											

Source: Modified from Volf 1978, Table XVI.

On balance, the therapy can be said to be worth considering for any case of significant potential for long-term effects. The reasons for the variability must lie partly in the very disparate dosage regimens, but some must reside in differences in chemical or physical form of the deposit or in factors not yet apparent.

A few of these cases are considered in some detail below to illustrate certain points. We will concentrate on work that extended over from significant to very long periods.

Probably the longest observation period concerns a twelve-year study in Pittsburgh of an individual exposed to ^{241}Am (Rosen et al. 1980). There had been earlier reports of both plutonium and americium from Pittsburgh (Wald et al. 1968) with interesting coincidence of body burdens measured by external counting and those derived from urinalysis, along with general recommendations for the management of contaminated cases. However, the one we choose to discuss represents the longest observation period in all of the reports. The case came to light through the discovery of alpha activity in urine specimens. In-vivo analysis in 1967 led to an estimate of a body burden of $1.8\ \mu\text{Ci}$ of ^{241}Am . Since the individual was working with americium oxide in powder form to prepare foils, the intake route was presumed to be inhalation. He was removed from the work in May 1967. In September 1967, weekly administrations of $(\text{CaNa}_3)\text{DTPA}$ were begun and were continued almost without interruption through 1974. Results were monitored by periodic measurements using in-vivo methods for the content of total body, skeleton, chest, and liver. Also, urine and feces were collected from September 1967 through December 1974, with spot samples subsequently, a monument to the dedication of both the workers and the patient. During therapy, average excretion rates in urine were increased by a factor of about ten. By the end of the reporting period, the body burden had been reduced to about $0.7\ \mu\text{Ci}$, considered to be mostly in the skeleton. No adverse effects from either the americium or the therapy could be found in liver or kidney function, cytogenetic status, or hematological status. The applicable permissible body burden at the time for ^{241}Am was $0.1\ \mu\text{Ci}$ with kidney as critical organ or $0.05\ \mu\text{Ci}$ with bone as critical organ. Therefore, this case, even with therapy, was well above limits even for occupational exposure and should be watched with care. Obviously, the reduction in body burden might have been much greater if the case had come to expert attention, and therapy had been instituted immediately.^(a) Nevertheless, there is no doubt that the therapy greatly reduced the liver content and removed in excess of one-half the body burden between 1967 and 1974.

A somewhat similar case of exposure to americium occurred in New York State. It has been followed by the workers at the New York University Institute of Environmental Medicine. The case involved a father and son exposure and thus provided an opportunity to compare both metabolism and therapy in the juvenile and the adult. The incident took place in the Albany, New York, area as the result of a home workshop project of the father and son. They were totally unaware of their contamination or that of their surroundings until it came to the attention of New York State Health Department authorities (Whalen and

(a) Therapy was begun very promptly after the situation was appraised, but an appreciable period elapsed before that, since time of exposure was estimated as having occurred in 1965 or early 1966.

Davies 1972).^(a) The contamination began in late 1963, and exposure may have continued until the problem was discovered in 1970. A fairly detailed report of the earlier findings was made at the IAEA symposium, Assessment of Radioactive Contamination in Man (Wrenn, Rosen, and Cohen 1972) and they continued in annual reports of the New York University Institute (Wrenn, Cohen, and Eisenbud 1977). The original source contained about 5 mCi of ^{241}Am .

In-vivo gamma-ray measurements were made of skull, lungs, and liver; radiochemical measurements were made of urine, feces, and blood. The only tissue samples obtained were deciduous teeth from the son saved by the family. Therapy with $\text{Na}_3(\text{Ca-DTPA})$ was initiated in 1970 and continued until 1976 in three separate installments, 1970, 1973, and 1975. In the 1977 progress report (Wrenn 1977), estimates were made that the ^{241}Am body burden of the adult had been reduced by 23% in six years, while the juvenile (ten years old in 1970) lost about 75% of the initial body burden. By 1976, the bulk of the body burden was in bone of both patients.

The NYU investigators took the opportunity afforded by this case to compare ^{241}Am metabolism in man to their ongoing work in baboons cited in section IV of this chapter. The conclusions (Cohen et al. 1976) are:

1. DTPA is much more effective in accelerating excretion of ^{241}Am in the juvenile, both man and baboon.
2. ^{241}Am removed from the skeleton by the DTPA treatment appears primarily in the urine of both species.
3. Excretion in feces is also enhanced in both species, but this was not primarily from skeletal tissues.
4. There was reasonable agreement between man and baboon on quantitative aspects.
5. The treatment depleted the tissue of zinc, again in both species, and resulted in inhibition of a zinc-activated enzyme.^(b)
6. The difference in mobility of ^{241}Am in the juvenile appeared even in the most recent chelation therapy period, when the juvenile was fifteen years old.

A general survey of research at New York University was given by Cohen (1981).

A further summary from this work was added to the published literature by Cohen, Lo Sasso, and Wrenn (1979). Estimation of the americium content of total body and three tissues and its change over a ninety-three-month period is shown in table 19.18 taken from this paper.

Note that the removal rate from skeleton was appreciable in the adult only in the first year, while some mobilization occurred in the adolescent at later times. Note also relatively larger amounts of americium in the liver of the adolescent as well as its continued mobilization.

One of the most dramatic incidents with americium occurred at Richland, Washington. An explosion at Hanford embedded contaminated debris and

(a) The father was an engineer with the New York State Health Department and was fully confident that the americium was firmly fixed in the source. It was through a routine check at the office that his clothing was found to be contaminated. Actually six members of the household were measured, but only the father and son had body burdens that prompted therapy.

(b) Later work indicated also depletion of manganese.

TABLE 19.18. Estimation and Sequential Measurements of ^{241}Am Distribution in an Adult Male and an Adolescent Male

Months Since April 1970(a)	Adult ^{241}Am Burden(b) (nCi)				Adolescent ^{241}Am Burden(b) (nCi)			
	Lung	Liver	Skeleton(c)	Total Body	Lung	Liver	Skeleton	Total Body
0	14.9	3.0	(70.1)72.1	90.0	7.8	10.0	17.9	36.4
12	15.5	2.6	(75.9)38.8	56.9	4.6	5.2	9.9	19.7
17	19.4	3.1	(74.7)33.6	56.1	4.0	5.2	13.9	23.1
29	12.7	4.9	(70.1)54.6	72.2	3.8	6.5	13.0	23.3
37	16.4	2.9	54.0	73.3	3.1	4.1	19.1	26.3
38	16.3	5.2	46.5	68.0	2.8	6.4	12.1	21.3
42	11.7	1.6	48.0	61.3	2.1	4.2	11.7	18.0
52	12.3	1.3	(40.2)42.4	56.0	0.3	3.8	14.7	18.8
57	10.4	0.7	(34.5)50.2	61.3	N.D.(d)	2.6	15.9	18.5
58	11.5	1.5	(40.2)41.3	54.3	0.3	1.8	10.1	12.2
75	9.3	0.4	(48.4)49.9	59.6	N.D.	2.3	10.7	13.0
93	9.3	1.5	(45.3)44.3	55.6	0.1	1.7	10.5	12.3

(a) Decorporation therapy was administered during the periods between months 0 and 12, 37 and 38, and 57 and 58.

(b) No error terms have been assigned to these values, since it was determined that unknown positioning consistency, body size variability, detector refabrication, and changing biological distribution of ^{241}Am will all account for errors that may be larger than counting statistics alone.

(c) Values in parentheses are determined by extrapolation of skull measurement. Other values are determined as skeleton = total body + lung + liver; values so obtained for 12 and 17 months may be in error because of detector refabrication and calibration change.

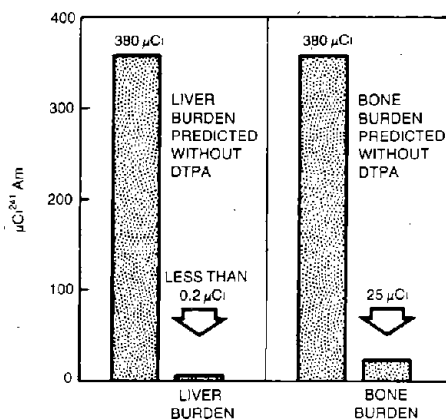
(d) Not determined.

Source: From Cohen, Lo Sasso, and Wrenn 1979. Reprinted with permission of Science, Washington, D.C., copyright 1979.

americium particles in the side of the head and face of a worker, Mr. McCluskey. The quantities were large. There is no question but the medical treatment, including chelation therapy, greatly extended the victim's life.

The first accounts appeared in a Pacific Northwest Laboratory report (Heid et al. 1979a), at which time the incident was two and one-half years old. This was repeated in an IAEA symposium paper published in the same year (Heid et al. 1979b). An idea of the extent of contamination and the importance of the chelation therapy is shown in figure 19.14.

FIGURE 19.14. Effectiveness of DTPA in reducing liver and bone burdens. (Redrawn from Heid et al. 1979a.)



A vivid description of the accident and of Mr. McCluskey's inspiring attitude and philosophy is contained in a lay press article in the *Reader's Digest* (Englehardt 1981) under the catchy title, "The Atomic Man." The article states that Mr. McCluskey was carrying over five hundred times the maximum allowable body burden of americium. While true, this is somewhat misleading, since much of the contamination represented americium buried in the skin and was thus somewhat superficial. However, part of the exposure was by inhalation also, so that the amounts are still enormous by any ordinary measure.

At a meeting of the Hanford Environmental Health Foundation Transuranium Registry in November 1982, the case was reviewed in depth, and the subject gave his personal version of the occurrences and his reaction to therapy.^(a) Pictures showing the extent of his injuries, which included damage to one eye, and his present appearance testified eloquently to the changes wrought. The data on the extent of contamination indicated that without treatment skin ulceration and the whole sad story of the early radiologists would have transpired as well as possible longer-term effects from the deposits in bone and liver.

A full scientific and clinical discussion of this case appears as a series of eleven papers prepared for a special issue of *Health Physics* (Thompson 1983). There are discussions of the facility, the medical management and chelation therapy, histologic and autoradiographic observations on skin, hematological changes, urinary excretion of trace metals, external decontamination procedures, radiation dose estimations, even the psychological aspects of the incident. It makes interesting and important reading.

Long-term follow up of therapy of *plutonium* contamination instances is documented in table 19.17. Nearly all show significant excretory multiplication factors. Dolphin (1976) makes special mention of a wound case described by Schofield et al. (1974) in the United Kingdom, where contamination was reduced first by surgical excision and then by extensive Ca-DTPA treatment. Because of breaks in the treatment periods, it was possible to establish quite clearly a phenomenon indicated by other work, viz., mobilization can occur at considerable periods after deposition, albeit with a reduced ratio between treated and untreated excretion rates.

In a summary table of sixteen United Kingdom cases, thirteen of them plutonium, one americium, one americium and curium, and one curium, the preponderance of evidence was that *clinical treatment could be successful for inhalation cases as well as for wounds*.

Worthy of special note is the use of the inhalation route for the administration of the chelator to humans. This began at Hanford (Smith 1979; see also case #17 in table 19.17, which was reported by Jech, Andersen, and Heid 1972). Small nebulizers were developed that greatly facilitated self-administration of the agent. A two-year study at the U.S. Savannah River plant (Jolly et al. 1972) made successful use of the nebulizer and shows a picture of it in use. It was also used at Savannah River for a curium inhalation incident (see case #39 in table 19.17), but without effect.

The Rocky Flats plant of the Dow Chemical Company fairly early reported on the results of up to two years of treatment after an acute intake of plutonium.

(a) He viewed everything that had been done as fully in his best interests and expressed gratitude for all that had been done.

Chelation accounted for removal of significant amounts (Piltingsrud 1964; Lagerquist et al. 1965; Lagerquist, Putzier, and Piltingsrud 1967). Indeed, one of the highest removal fractions in man was reported by Lagerquist, Allen, and Holman (1967) in treatment of a contaminated nitric acid burn at Rocky Flats. This was based on comparing the remaining body burden predicted from the Langham equation (chapter 16) and the amount excreted. It came to 96.5% removal! This is probably high but may represent unusual mobility of contamination from a burn area.

In earlier work, the Rocky Flats group compared the effectiveness of DTPA in a case of ingestion plus inhalation plus small acid burns to a simple small wound. Surprisingly, the effectiveness was much greater for the inhalation case. This illustrates a point brought out by others (e.g., Parker 1973) that the mobility of material from contaminated wounds can be quite variable and unpredictable.

The Rocky Flats people developed a useful "wound counter" for plutonium. Such instruments evidently developed independently elsewhere or found their way to other laboratories. Parker (1973) describes use of such an instrument, and it appears to have been in long use at Hanford.

Finally, we should mention the only case of pulmonary lavage recorded for the removal of plutonium in man. The work was done at the Lovelace Clinic in Albuquerque and the Inhalation Toxicology Research Institute on an individual with an estimated lung burden of 450 nCi of ^{239}Pu (McClellan et al. 1972a,b). It appeared in print only as an abstract but was discussed in some detail at the Seventeenth Annual Meeting of the Health Physics Society and at contemporary symposia. In addition to lavage, the subject received DTPA beginning on the eighth day postexposure. A total of 146 nCi of ^{239}Pu (plus a little ^{241}Am) were removed in eleven days of treatment: 59 nCi were recovered from the lavage fluid associated primarily with pulmonary macrophages, and 87 nCi appeared in excreta. The authors were satisfied that pulmonary lavage was a useful adjunct therapy. However, these results and others on man described above do not support the statement made from the animal work that lavage was the only effective way to remove radionuclides deposited in the lungs. Indeed, several of the cases of inhalation exposure quoted above from various laboratories indicate more mobilization of lung deposits in man by the chelators than would have been predicted from the animal experiments. Curiously, the investigators do not remark on this conceivably important difference.

4. Conclusions Regarding Clinical Experiences

This review of the efficacy of various therapeutic regimens for removal of deposited radionuclides in humans shows that by and large the research done first with animals was confirmed and extended in man. There were only a few instances of disagreement, and these tended toward greater rather than less efficacy in humans. Matters of toxicity and pharmacological comparisons will be reserved for the next section.

Despite the relatively low frequency of serious contamination incidents, a formidable body of knowledge has been put together. The NCRP report (NCRP 1980) gives a detailed discussion of treatment for internal contamination under the following broad headings:

Procedures to Reduce Gastrointestinal Absorption

Stomach-Lavage, Emetics, Purgatives, Ion Exchange Resins, Prussian Blue, Aluminum-containing Antacids, Alginates, Barium Sulfate, and Phytates

Blocking and Diluting Agents

Iodides, Strontium Compounds, Phosphate, Calcium, Zinc, Potassium, and Forced Fluids (for tritium)

Mobilizing Agents

Antithyroid Drugs, Ammonium Chloride, Diuretics, Expectorants and Inhalants, Parathyroid Extract, Corticosteroids

Chelating Agents [the longest section]

EDTA; DTPA [in various forms such as Ca-DTPA, Zn-DTPA]; Penicillamine; Deferoxamine

Lung Lavage^(a)

Finally, as an indication of the value attached to *prompt* therapy, in at least one country, it is reported that the French installations have "do-it-yourself" kits conveniently located near work stations. Each kit is for rapid self-therapy if a contaminating event is suspected. There are different kits for different types of exposure (inhalation, wound, etc.). This extent of preparation bespeaks considerable anticipated clinical usefulness for the procedures developed.

As might be expected, enthusiasm for these therapies (e.g., chelators) is not universal. Perhaps most outspoken was the group at Los Alamos, which has used chelators hardly at all for plutonium except for the early days when Harry Foreman was at the laboratory. Indeed, they questioned both the efficacy and safety of DTPA in 1968 (Schulte and Whipple 1968). Some of their reluctance seems to stem from one of the early cases described by Foreman, a female technician who showed large amounts of albumin in urine during the treatment period. Furthermore, she suffered ill health from then on, although no true causal connection could be shown between the treatment and subsequent ill health. They also cite other cases, which had barely detectable increases in excretion of plutonium, and felt that the early treatment interfered with evaluation of the true body burden and thus the seriousness of the incident. The paper by Schulte and Whipple established that the renal damage was not permanent and that the subsequent ill health was probably not related to the therapy. However, all seemed to agree to the need for conservatism in application until more research had been done. As we have seen, ample additional work has been completed, and chelation therapy has been applied to many other areas in addition to radionuclide depositions, but the fact remains that establishment of the presence of significant risk from the deposition is a *sine qua non* for instigation of therapy.

VI. Pharmacology and Toxicology of the Main-Line Chelators

The radioisotope toxicology establishment had to enter upon much research ordinarily associated with more conventional facets of pharmacology in order to work intelligently with the chelating agents. Likewise, much about the toxicology of the agents themselves had to be learned. The investigators had ample

(a) The approach in this section of the document is largely clinical, but it is clear much of the clinical work depended on the laboratory research. However, much of it came from general medical research and cannot be entirely credited to the groups and efforts we have reviewed in this chapter. For quick reference the reader is again referred to the table at the beginning of the NCRP report.

company among those interested in chelators—either as clinical tools in specific diseases, an area we must neglect entirely, or for treatment of heavy-metal poisoning.^(a) Nevertheless, some of the groups we have met in earlier sections found it advisable to pause for study of the agents themselves before undertaking further efforts at therapy. This was done as part of the internal emitter programs supported by the AEC and its successor agencies until the cutoff of funding initiated in the summer of 1979. The results have inherent interest and extend in significance beyond the problems of therapeutic removal of radionuclides.

There were efforts quite early to understand how the various agents behaved in the body (we are labeling these *pharmacology*) as well as any untoward or unexpected effects (we are labeling these *toxicology*). There was work with nearly all of the substances and procedures described earlier in this chapter. However, the area of greatest concentration involved the polyamino-polycarboxylic-acid-type compounds like EDTA, DTPA, etc., which we have discussed above under the rubric “Main-Line Chelators.”

A. Pharmacology (Pharmacokinetics, Pharmacodynamics)^(b)

The story starts at the same time and in the same places as the consideration of chelating efficiency for the removal of radionuclides. It was based upon strong and extensive experimental work done in the chemistry departments of industry and academe, which we have already alluded to, referenced, and discussed briefly. Some principles of the pharmacology of the agents emerged early (Foreman 1954, 1955, 1960; Schroeder 1960; Schubert 1954). A few of them are:

1. Stability constants measured in the test tube can frequently predict which elements are likely to be chelated and removed and which are not.
2. The positive predictions from the test tube do not necessarily follow exactly in vivo. The chelating agent must compete with “naturally occurring binding forces whether these be insoluble crystalline material in the skeleton, the forces by which the reticuloendothelial system binds materials (whatever they are) or the many naturally occurring complexing or chelating agents.” (Foreman 1954).
3. The agent must have a strong binding tendency for the metal to be removed, and the binding must be appreciably higher for it than the forces for naturally occurring essential metals to be of any real use.
4. The metal chelate must be readily excreted.
5. Stability constants measured under nonphysiological conditions are of little use.

It soon became apparent that EDTA was poorly absorbed from the gastrointestinal tract (Foreman 1960). This may be because EDTA has its iso-electric point at about pH 1.2. It may become quite insoluble at the pH of the stomach

(a) One of the broader overviews of both aspects of chelation and of its chemistry can be found in the excellent book by Albert, now in its sixth edition (Albert 1979).

(b) Some of the work borders closely on therapy, but we will consider it primarily pharmacological.

contents and be solubilized only slowly as it passes through the small and large intestines.^(a)

It appears that EDTA is not broken down (metabolized) in the body and is not conjugated like most drugs (Schroeder 1960) except for its combination with metals. For example, practically no $^{14}\text{CO}_2$ appeared in expired air after administration of EDTA labeled with ^{14}C . As a result, it is almost totally excreted, mostly in the urine if entrance is parenteral, mostly in feces if entrance is by mouth. This was found by Foreman and his group at Los Alamos using ^{14}C -labeled EDTA. Typical findings in the rat are shown in table 19.19, taken from Foreman (1953).

TABLE 19.19. Distribution of CaNa_2EDTA at Various Time Periods After Administration^(a)

Tissue or Sample	1½ hr After I.P. Injection	6 hr After I.P. Injection	6 hr After I.P. Injection ^(b)	24 hr After I.P. Injection	24 hr After Oral Adm.
Urine	85.22	95.73	96.66	94.56	10.30
Feces ^(c)	0.50	2.04	1.20	3.63	88.32
Expired CO_2		0.05	0.10	0.08	
Skin	2.38	0.83	0.84	0.25	0.16
Kidney	1.36	0.34	0.26	0.27	0.04
G.I. Tract	0.22	0.15	0.17	0.72	0.45
Liver	0.46	0.15	0.19	0.05	0.18
Skeleton ^(d)		0.30		0.12	0.08
Muscle ^(e)		0.13		0.28	0.36
Blood	1.65	0.07	0.04	0.01	0.04
Remains ^(f)	8.08	0.03	0.09	0.01	0.03

(a) Results are expressed in per cent of recovered dose per total organ or sample.

(b) 250 mg inert CaNa_2EDTA added to study effect of size of dose.

(c) Feces include contents of gastrointestinal tract at time of sacrifice.

(d) Calculations based on assumption that the skeleton equals 18 per cent of the body weight.

(e) Calculations based on assumption that the total muscle mass equals 40 per cent of the body weight.

(f) Includes heart, lungs, spleen, brain, gonads, adrenals and thymus, all of which were assayed separately but not reported individually, since none of these organs contained over 0.05 per cent, except in the 1½ hr period.

Source. From Foreman 1953b. Reprinted with permission of the Journal of the American Pharmaceutical Association, Washington, D.C., copyright 1953.

The behavior extended to other species including man (Foreman, Fuqua, and Norwood 1954) and to the other main-line chelators available (Foreman 1960).

(a) The people at Hanford (Baxter and Sullivan 1972) found that plutonium chelated with DTPA was absorbed from the intestine to a much greater extent (by a factor of about seven hundred) than unchelated plutonium. This may appear to be in conflict with the finding that EDTA (and DTPA) themselves are poorly absorbed. It is not in conflict because plutonium is so very insoluble that it does not take a very large absolute increase in numbers of molecules crossing the intestinal barrier to accomplish an amplification factor of the magnitude found. Also, the number of chelate molecules binding plutonium is still a small fraction of the oral dose.

Only a few compounds, those with lyophilic properties, discussed earlier, which were developed for special purposes, have significantly different distribution patterns.

Blood activity of $\text{Ca }^{14}\text{C EDTA}$ peaked at about 1% of the injected dose per cubic centimeter of blood immediately after intravenous administration. However, it fell rapidly to less than 0.001% at seven hours in the rat. Amounts after intramuscular or intraperitoneal administration peaked around 0.4% at about one hour and then fell rapidly also. After oral administration, the blood level never reached more than 0.04% (Foreman 1953).

As indicated earlier, penetration of EDTA into cells, even the red blood cell, was found to be minuscule. The substance came rapidly into equilibrium with a fluid volume slightly larger than the extracellular space, and then left rapidly as any very soluble substance does. Renal clearances were between 1 and 1.5 ml/min.

All of this led the investigators to the conclusion that multiple doses, or slow-drip infusions, would be needed to maintain an effective blood level of the chelator, and this was, of course, what was found in the experimental work described earlier. However, there were problems with this. There resulted a considerable volume of work on various dosage regimens and forms, extending over many years. Whereas the early work had been concentrated at Los Alamos and Hanford, the later efforts were more ubiquitously distributed in the United States, in Europe, and in the USSR.

Some of the work presented surprises. For example, even discounting relative toxicity, lower doses of chelator were sometimes more efficient at metal removal than higher doses. This led Foreman to speculate that "somewhere along the transport chain there is a membrane whose transfer potential for Ca-EDTA is saturated at low concentrations" (Foreman 1962, p. 356).

Catsch (1962) addressed the general principles of both the chemistry and pharmacology of several chelators in several dosage patterns. His primary conclusion using work done at Karlsruhe was that early application was of greater importance than the time pattern of dosage thereafter. However, as we already know, too much too soon can be toxic.

Despite the fact that the main body of the chelator molecule is not broken down by metabolism in the body, the binding to metal can be altered relatively easily, and free metal can be released *in vivo* (Foreman 1955).^(a)

In 1969, the Argonne group addressed the problem of effective dose regimen (Rosenthal et al. 1969). They tried DTPA doses spaced at three-day intervals and measured mobilization of plutonium in mice. The spaced doses were more effective, particularly for removing plutonium from liver. However, this does not address the prevention of deposition in bone by having a high blood level of chelator present early.

The Utah group became deeply involved with all aspects of chelation therapy beginning in the mid-1970s. We have already seen some of their results. In one of the annual reports issued soon after this work began, Stevens et al. (1974) considered alternate schemes for administering chelating agents based upon their solubility in lipids. Modifications of structure expected to aid penetration into cells reduced mobility of chelators but also reduced their effectiveness.

(a) This applies primarily to "foreign" metals. Normally occurring trace metals, with the possible exception of zinc, seem to be very firmly bound *in vivo* normally and can be removed only with difficulty.

Calder et al. (1978, 1979), also at Utah, tried a slow-release implant form of Zn-DTPA. They combined the Zn-DTPA in dried powder form with propylene-glycol 4000, beeswax, and peanut oil and implanted various types of pellets subcutaneously. The results were encouraging in terms of the basic problem of maintaining an effective blood level of chelator. But there were foreign body reactions at the implant site. Also, the implant required surgery, not a clearly advantageous trade-off with intravenous injection. They proposed to continue the work and develop better implants, but the funds were cut off and the work stopped.

In the same year, the Utah group (Lloyd et al. 1978) investigated the different frequencies of administration. They concluded that daily injections of Zn-DTPA are more effective for removing incorporated plutonium (in the beagle) than weekly injections of Ca-DTPA and were better tolerated because of the lower toxicity of Zn-DTPA.

In yet another study at Utah, Lloyd et al. (1979) researched the dependency of chelation efficiency upon time after the first injection. They tried to quantify the magnitude of the decrease in efficiency produced by delay in initiation of therapy with DTPA. The delays were from one minute to three days. The effect was more pronounced for removal of americium than for plutonium, but was significant for both. The retention in liver, kidney, spleen, and whole body is shown in table 19.20.

TABLE 19.20. Retention of Injected ^{241}Am or $^{237+239}\text{Pu}$ at 7 Days After Administration of 300 μmole of Ca-DTPA(a)

Dog	Age (months)	Injected Ca-DTPA ($\mu\text{mol/kg}$)	Delay to DTPA	Radionuclide Retention (%)			
				Total Body	Liver	Kidneys	Spleen
— Americium —							
T168W4	33	31	1 min	2.7	0.69	0.12	0.01
T169W4	31	29	6 min	10	4.1	0.26	0.02
T170W4	32	29	30 min	29	12	1.8	0.04
T171W4	28	33	150 min	45	16	1.0	0.07
T172W4	29	26	8 hr	58	26	1.6	0.12
T173W4	31	26	1 day	73	39	1.0	0.10
T174W4	33	35	3 days	72	39	1.0	0.05
— Plutonium —							
T206P2	42	27	1 min	31	7.2	0.42	0.35
T207P2	31	33	6 min	28	5.6	0.28	0.26
T208P2	31	28	30 min	34	7.7	0.34	0.26
T209P2	31	31	150 min	44	11	0.42	0.41
T210P2	31	32	8 hr	52	11	0.42	0.45
T211P2	43	40	1 day	50	14	0.52	0.36
T212P2	26	34	3 days	70	26	0.56	0.54

(a) Differences in total-body retention derived by in vivo counting and excreta assay averaged about 2% of the injected ^{241}Am and 3% of the injected ^{237}Pu .

Source: Modified from Lloyd et al. 1979. Reprinted with permission of Academic Press, Orlando, Florida, copyright 1979.

Looking in detail at bone (humeri), it appeared that early treatment had a disproportionately greater effect in reducing the content of ^{239}Pu in trabecular bone. Since this is the area where most bone tumors of the sarcoma type arise, the result is significant. The authors urge, on the basis of this and earlier work, that in a case of human exposure a large dose (1 to 2 g) of Ca-DTPA be given as soon as possible. This should be followed by a series of Zn-DTPA injections but with gradual lengthening of the interval.

The switch from calcium to zinc salt is based on the fact that the calcium salt is very effective when given initially in a large dose, while the zinc salt is better tolerated over a series of injections, even though it is not quite as effective.^(a) They urge continuing treatment, however, if there is much chance of translocation of deposits from lung or from a wound to the blood and hence to liver and/or bone.

The quest for a really effective regime for giving the EDTA-DTPA-type chelators orally has continued, especially in European laboratories (e.g., Taylor and Volf 1980). The complexity of the results and their application to therapeutics can be gleaned from the abstract of their paper, quoted below:

Abstract—The effect of orally administered chelating agents (DTPA, TTHA, TPHA, DFOA) on injected ^{239}Pu and ^{241}Am was studied in rats. Preliminary experiments with chelates given by stomach tube indicated that TTHA was the most promising agent for reducing retention of ^{239}Pu , but when the chelates were administered at lower concentrations in drinking water, DTPA proved equal or superior to TTHA in reducing the tissue content of ^{239}Pu and ^{241}Am : the calcium- and zinc-chelates of both DTPA and TTHA were equally effective. Prolonged, delayed addition of Zn-DTPA to drinking water (from day 4 to 25 post ^{239}Pu) at various concentrations revealed an exponential dose-effect relationship with respect to the total amount of Zn-DTPA offered, but irrespective of whether it was administered in 9 or 21 fractions. Up to one half and three quarters of the ^{239}Pu could be removed from the skeleton and liver, respectively. In order to achieve an equal effect on ^{239}Pu retention, about 30 times more Zn-DTPA had to be added to drinking water than the amount of Ca-DTPA injected. However, drinking Zn-DTPA [sic] in amounts only about 3 times as high as those of injected Ca-DTPA proved effective in reducing the tissue contents of ^{239}Pu . There was no evidence of toxicity in rats exposed to up to 30 mmoles Zn-DTPA in drinking water.

(Taylor and Volf 1980)

Also, the quest for derivatives with greater cell penetration described briefly in section VI has continued as a basic pharmacological problem on both sides of the Atlantic (e.g., Bulman and Griffin 1981, Harwell; Mays et al., 1981, Utah). Of particular interest is the calculation by Mays and coworkers of the minuscule amount of chelator that needs to penetrate cells to bind *all* of the plutonium present in a subject with a maximum permissible body burden of $0.04\ \mu\text{Ci}$ even if *all* of it is inside cells. With only 0.5% penetration of cells from a typical 1-g dose, the number of chelator molecules would exceed the number of plutonium atoms by a factor of four thousand!

(a) This was shown in beagles by Lloyd et al. (1977) at Utah and emphasized by Catsch on many occasions from review of Karlsruhe and Utah work. We will cite details in the next section.

Mays and colleagues point out that we really do not know in sufficient detail the amount of DTPA that enters cells of various types. They suggest careful tracer experiments to ascertain this fraction accurately, since it does not need to be large to be important. The Utah group also suggests that the process of pinocytosis (uptake into cells of very small droplets of fluid by an in-folding and pinching off of the cellular membrane) may play a part in cellular uptake of chelators, as of many other substances.

It will be noted in table 19.12 and earlier tables that the percentage of plutonium that is ultrafilterable is recorded beside many of the experiments. Throughout the work on chelation of the transuranics, especially plutonium, a distinction has been made between monomeric and polymeric forms of the radionuclides. This is on the theory that the monomeric form, i.e., ultrafilterable and thus either ionic or in very small aggregates of atoms, is handled differently from polymeric forms, which will have the properties of colloidal aggregates (chapter 4). The latter will be subjected to phagocytosis, trapped by the reticuloendothelial system, etc., while the monomeric form will not. Obviously, a really sophisticated system of therapy might aim in different directions if it were known that the material to be decorporated was predominately in one or the other form. Much very interesting animal research has been done around these postulates, but it has contributed more to our knowledge of the pharmacokinetics of radionuclides than to therapeutic regimens. For one thing, the distribution between monomeric and polymeric forms is subject to considerable change with time. Further, it is not easy to determine the relative proportions of deposited radionuclides in different forms in a case coming in for therapy. Thus, the approaches had to remain quite broad, indeed somewhat empirical.

We will complete this section with a quick review of some of the pharmacological aspects of removal of deposited metals from the lung.

With the development of ideas for administering chelators as aerosols, it became important to know the extent and rapidity of their absorption from the lung. It was determined fairly early at Hanford that there was substantial absorption of these entities on inhalation. A careful quantitative evaluation came from the Lovelace group several years later (Dudley, Muggenburg, and Cuddihy 1978). A solution of DTPA labeled with ^{111}In was administered to beagle dogs, and its absorption and translocation from various segments of the respiratory tract were measured. Percentage absorption after twelve to twenty-four hours were 16%, 48%, and 90% of the amount instilled directly into nasopharyngeal, tracheobronchial, and pulmonary regions, respectively. (Fiberoptic bronchoscopy was used for the deeper instillations.) Material inhaled into the upper respiratory tract as an aerosol was absorbed to a somewhat greater extent (23% versus 16% for the deep instillation). In both cases, there was longer retention in the blood stream after entry via the lungs than after intravenous injection, and appreciable amounts remained in lung. This work confirms earlier work done with rats in the United Kingdom (Stather et al. 1976).

The fraction absorbed from the upper respiratory tract, while not large, was considered significant and an important factor in favor of the inhalation/instillation route of administration, especially when coupled with the greater and longer blood retention times. Specifically, the chelator need not reach the deep lung to provide significant blood levels. Also, the presence of DTPA in lung as long as forty-eight hours after instillation was considered an important adjunct to possible reactions in lung with deposited radionuclides.

In this work, we see, as we have in other connections, that absorption from lung may be rather different from gastrointestinal tract absorption. In contrast to the very poor absorption of EDTA and DTPA from gut that we noted earlier in this section, the total absorption from lung was estimated at about 20%.^(a)

It is clear that basic research on the pharmacology of the chelators is far from finished.

B. Toxicology of the Main-Line Chelators

The fact that agents like EDTA and DTPA had inherent toxicity became apparent quite early in their use. Unfortunately, this occurred before the days of the stringent toxicity tests we are now accustomed to expect before any new drug can be used clinically. Therefore, some of the earliest signs of trouble turned up in clinical uses, albeit not ones for removal of radionuclides.

1. Kidney Damage

The first manifestations of unexpected toxicity were seen in patients receiving EDTA for reduction of calcium deposits in the body associated with metastatic cancer and in patients undergoing therapy for lead poisoning. Fairly severe damage appeared in kidney tubules in some patients receiving large doses of EDTA. There were two cases at MGH, both terminal patients, who came to autopsy (see Foreman, Fuqua, and Norwood 1954) and a case at Los Alamos (Foreman, Finnegan, and Lushbaugh 1956) of a worker who developed clinical signs of kidney dysfunction that reversed on cessation of DTPA treatment. Other earlier human cases are referenced by Foreman, Fuqua, and Norwood (1954) and discussed in detail by Seven (1960). There is even the possibility that the unexpected kidney damage contributed to the deaths of one or more of the terminal patients.

It became clear that the kidney lesion could be reproduced in rats (Foreman, Finnegan, and Lushbaugh 1956). It was a "toxic nephrosis consisting of severe hydropic degeneration of the proximal tubules." It could extend through other parts of the kidney structure even to the distal tubule with high doses or long-continued administration. However, it was surprisingly reversible after the injections were stopped. These lesions have been described repeatedly (Foreman 1960, 1962) and found to occur with DTPA as well as with EDTA.

There was considerable interest in the mechanisms of this effect. Some of the work was done within the internal emitter establishment, especially at Los Alamos, but much was also done in centers interested in therapy for heavy metals in general. It was tempting to relate the effects to removal of essential trace metals, possibly from enzyme systems. Alternatively, especially in the presence of complexes of mercury or other kidney poisons that might dissociate at the low pH of the kidney tubule (recall the role played by such processes in the toxicity of uranium described in chapter 2), a direct heavy-metal poisoning might play a role. At the symposium on metal binding in medicine held at Hahnemann Medical College, and already cited several times, Dr. Frederic Reiders

(a) In the same experiment, a dog receiving DTPA by gastric lavage absorbed about 8%, slightly more than that reported for rats or humans, but still well below the lung absorption.

from the Pennsylvania Department of Health suggested that zinc might be the essential trace metal mobilized by the chelator (see Schroeder 1960).

In the same discussion, Foreman described quantitation of the renal lesion in animals, by the so-called ED_{50} (effective dose in 50% of the animals). It was about 60 mg/kg, well above the minimal therapeutic level, but within the upper range of an active decorporation program. There did seem to be a threshold for the effects.

The doses required were sufficiently above the therapeutic level not to discourage use of the chelators except for contraindication of their use in the presence of nephritis. Also, in view of the reversibility of the lesions, it was suggested that the chelators be given in short courses with periods of rest interspersed.

In a later fuller discussion at a symposium held at Richland, Foreman and Nigrovic (1968) described additional work. Apparently the kidney lesion was much less likely to develop with Zn-DTPA. This was regarded as confirmation of the idea that zinc mobilization was important (e.g., removal from the zinc-dependent alkaline phosphatase enzyme). However, the toxicity of a manganese chelate (Mn-DTPA) was also lower than that of conventional sodium or calcium EDTA or DTPA.

2. Hypocalcemia

The possible upset of calcium homeostasis by these chelators has been alluded to many times already. Obviously, too rapid administration could produce tetany and convulsions. However, replenishment of calcium from body stores is sufficiently rapid that infusions at rates up to 15 mg/min of EDTA usually produce no marked changes in serum calcium level or symptoms of low blood calcium (Seven 1960). There is, however, marked variability in the response of different individuals.

Obviously, the addition of calcium to the solution helped considerably along with care in the infusion rate. Indeed, more rapid infusions are possible without hypocalcemia if the calcium chelators are administered (Seven 1960).

Symptoms like numbness and tingling in the fingers and around the mouth and face frequently follow these chelate infusions. These are like early symptoms of decreased serum calcium levels. However, they seem to persist even when the calcium chelate is given, a subject for further investigation.

3. Acute Lethality

These substances do not rate as chemical toxins of high potency. Yet, a few people have investigated their acute and subacute toxicity, and it was begun soon after the agents appeared on the scene. The first work was done by a group at the Department of Pharmacology of the Boston University School of Medicine (Bayer et al. 1952). They did both Ca-EDTA and Pb-EDTA. Acute lethality, i.e., a conventional LD_{50} , was difficult to obtain because the large amounts of material required frequently could not be brought into solution easily. Nevertheless, LD_{50} values were estimated. They were about 6 g/kg in mice, rats, and rabbits for intraperitoneal doses, less than 4 g/kg in rabbits after intravenous administration with no deaths at 2 g/kg. On repeated doses for 14 wk, these numbers were reduced to about 0.5 to 0.25 g/kg. Five doses per week were not toxic to rabbits over 105 days at levels of 20 to 40 mg/kg, but definitely toxic at daily doses of 70 to 100 mg/kg. The report is in abstract form and does not give details regarding the symptomatology or causes of death.

This Boston work does not seem to have attracted much attention among those engaged in the researches we have been discussing in this chapter. However, slightly later work at Utah, in the United Kingdom, and in West Germany did attract attention in the radionuclide chelation circles. Morgan and Smith in the United Kingdom (1974a,b) found considerable damage in liver, kidney, and duodenum and did acute lethality determinations. Extrapolation of their LD_{50} figures from mouse to humans predicted a value for acute toxicity of 660 g for Ca-DTPA. There was little effect of chronic doses equivalent to 10 g.

At Utah, Taylor and coworkers (1974) showed that injections of Ca-EDTA of 0.16 g at five-hour intervals caused death in beagles by four days. The lethality was attributed to removal of zinc. Much lower doses (up to 0.36 mmole/kg produced no symptoms except slight melena [blood in feces]).

At Karlsruhe, Planas-Bohne and Lohbreier (1976) used DTPA as both calcium and zinc salts and worked with rats. Forty-four weeks of treatment at 100 moles/kg twice weekly produced no adverse effects with either the zinc or the calcium salt. Continuous infusion brought about the typical toxic effects with the calcium salt but not with the zinc chelate. Repeated injections were not nearly as toxic as continuous infusion.

Of special interest is the finding that several dose fractions of Ca-DTPA were more toxic than single injections of the same amount. American and West German work contributed to this finding. Taylor and colleagues at the University of Utah gave 5.8 μ moles of $Na_3CaDTPA$ every five hours. The treatment was fatal within four days at a total dose of only about 8 μ moles/kg. Planas-Bohne and Ebel (1975) found also that several dose fractions of Ca-DTPA were more toxic than single injections of the same magnitude.

The reason (or reasons) for this phenomenon has not been proven. Obviously, the rapid excretion of EDTA- and DTPA-type chelators means that a single dose may leave quickly, thus allowing time for homeostatic recovery, while more sustained dosages deplete essential trace metals necessary for enzyme function.^(a) The Utah work takes up possible mechanisms in some detail.

These acute toxicity studies indicate a satisfactory but not a large therapeutic margin for the calcium and zinc salts, probably an insufficient margin for the sodium salt, that is, of course, not used anyway. Catsch (1976) remarks that the toxic doses of Ca-DTPA are fifty to one hundred times higher than the usual therapeutic dose. However, if the concentration in blood is maintained constant over a long time, the margin of safety narrows sharply, indeed to the point where continuous use of Ca-EDTA should be interdicted.

4. Relative Toxicity of Zn-DTPA

The idea of overtly substituting zinc for calcium in DTPA salts seems to have evolved largely in European laboratories. Among the principals was the group at Karlsruhe (Catsch, Seidel, Volf, et al.). If the toxicity of EDTA and DTPA involves zinc removal, as already discussed, the addition of zinc should counteract these effects and lower the toxicity. In a series of reports in the German literature, this premise was proved to be true for both lethality and toxic effects. Nevertheless, much attention had to be given also to the relative effectiveness. The best

(a) As we will see presently, inhibition of several enzyme systems, including DNA synthesis, has been recorded.

entrance into these developments for American workers is the summary paper by Seidel and Volf (1972) given at a Hanford symposium, Biological Implications of the Transuranium Elements. This work used rats and concluded that the two chelators were not very different in effectiveness (not in total agreement with later ideas) but that the zinc compound was distinctly less toxic (based on earlier work of Catsch [1964] and Catsch and Van Wedelstaedt [1965]).

Even the cumulative LD₅₀ for Zn-DTPA was about thirty times higher than that for Ca-DTPA, a severe test (Catsch 1976).

In the early 1970s, workers in the United Kingdom (Taylor and Jones 1972) also noted the lesser toxicity of Zn-DTPA and showed that there was transient inhibition of DNA synthesis in intestinal crypt cells by the calcium chelates but not by the zinc salt (see also Bohne 1972, quoted in Taylor et al. 1974).

In the United States, the Hanford group became interested quite early in Zn-DTPA. It was mentioned as a promising possibility by Norwood in the 1960s. However, most of their work was directed at relative effectiveness rather than at toxicity per se, except after inhalation.

The Utah group came down hard on the relative toxicities of calcium and zinc salts of DTPA as part of their extensive involvement with chelation research in the mid-to-late 1970s. There was an early paper in the annual report that showed low toxicity for the zinc salt; Lloyd and coworkers were so impressed by the lower toxicity of Zn-DTPA that they said, "We recommend that Zn-DTPA should replace Ca-DTPA as the treatment of choice, especially for protracted therapy in human cases" (Lloyd et al. 1977, pp. 93-94). Interestingly, this was at about the time that Catsch was backwatering some^(a) on Zn-DTPA because of findings showing lesser effectiveness, compared to the calcium salt. The Utah people used ²⁴¹Am in beagles as their test system and could find no real difference in effectiveness. The difference in toxicity was definite.

5. Effects on the Embryo and Fetus

These substances are teratogenic and considerably more toxic to the embryo and fetus than to the adult animal.

One of the earlier statements to this effect came from Norman Cohen at New York University in an annual report (Cohen and Guilmette 1974) and in a discussion session at the IAEA seminar, Diagnosis and Treatment of Incorporated Radionuclides (Cohen 1976).

The Utah group engaged deeply in the subject as part of their chelation research program. Fisher, Mays, and Taylor (1975)^(b) described toxicity of Ca-EDTA to the mouse fetus. At the high dose of 2.9 mmoles/kg there were no pups born. Only one fetus was found, and it was dead. A lower level of 0.36 mmole/kg had no apparent effect. This lowest level is still a factor of ten above the then-recommended daily dosage for humans, but the authors warn against incautious application of this apparent safety factor to human therapy because of the more rapid elimination rate of DTPA by rodents. Studies with Zn-DTPA were carried out in pregnant mice by Brummett and Mays (1977).

(a) Despite being regarded as the original promotor of the zinc salt.

(b) These authors quote somewhat earlier work on reproductive function and fetal development by Hurley and coauthors. This was contained in sources not available to the author.

Doses of the zinc chelate had no apparent effects on mouse fecundity or embryos or fetuses.

The zinc chelate was studied in more detail the next year—again using mice (Brummett and Mays 1977). This time, fetal toxicity was noted for Zn-DTPA, but it required a much higher dose. The lowest dose causing fetal damage in five days of treatment was 720 $\mu\text{moles/kg/day}$ for Ca-DTPA and 11,520 $\mu\text{moles/kg/day}$ for Zn-DTPA, a factor of sixteen larger. Also, while both agents caused abortions, fetal malformations (exencephaly) were found only with the calcium salt.

By the next year, the occurrence of fetal injury in two dogs was reported (Taylor and Mays 1978). The doses (30 $\mu\text{moles/kg}$) were injected each day starting at fifteen days after the first mating and continuing to birth of the pups. This dose had no detectable effect on the mother. Even the slight melena noted in nonpregnant animals did not occur. By contrast, the fetuses showed depressed birth weight (only one in five pups showed permanent stunting, however), changes in hair color to a silver-gray instead of the usual light brown (the normal pigmentation returned at three to four weeks of age), and there was definitely increased mortality of the pups in the first few weeks. Nearly all blood parameters were normal except for a variable degree of neutropenia (loss of white blood cells).^(a)

The Utah group became concerned that some of the toxic effects seen were resident in the method of preparation of their Zn-DTPA. They had been preparing the drug locally, and it contained 2 moles of sodium chloride for every mole of Zn-DTPA. On the other hand, material prepared for human therapy by the Sigma Chemical Company utilized a different process and was "a special batch of pure Zn-DTPA." A fairly extensive experiment was mounted in the mouse, not only to compare the two preparations but to investigate still higher levels of Zn-DTPA on the fetus (Calder et al. 1979). Acute effects were noted among dams at the highest Zn-DTPA dosage of laboratory-prepared agent. In fact, these animals died with severe kidney damage. There was some weight deficiency at birth in the pups at the highest level of either preparation, but no congenital malformations at all. The conclusion was that the "pure" preparation was even less toxic than the laboratory one, that the difference was not solely due to the sodium chloride, and that about four hundred times the prescribed dose for humans was needed to lower pup weights or cause kidney dysfunction in the mother. However, even longer-term experiments studying life span are needed and were planned, but abandoned by the cutoff of funds.

The Utah group, fairly early in their work on embryo and fetal toxicity, attempted an extrapolation of the finding on animals to the possible toxicity of Ca-DTPA to the human fetus (Mays, Taylor, and Fisher 1976). They concluded that Ca-DTPA did not have sufficient therapeutic margin to be used safely in pregnant humans. On the other hand, they felt that margin of safety for Zn-DTPA was adequate, though not large.

As we have seen throughout this book, Sikov and his colleagues at Richland have made a career of studying effects of radionuclides on the fetal and juvenile mammal. They worked with DTPA at about the same time as the Utah group (Sikov, Smith, and Mahlum 1975). As reported in an annual progress report, they

(a) This and the disorder of hair pigmentation seem to be related to what has been termed "the grey collie syndrome." It was postulated that this may have been due to chelation of copper.

found that one or two injections of 230 $\mu\text{moles/kg}$ Ca-DTPA had little effect, but 460 $\mu\text{moles/kg}$ were sufficient to kill the rat fetus. The injections were intraperitoneal given once a day on gestational days eight through twelve.

It is clear that these agents are more toxic to the embryo and fetus than to the adult and that chelation therapy of the pregnant human should be applied with caution and probably be limited to Zn-DTPA.

6. Pulmonary Toxicology

Reference to the extensive discussion of pulmonary toxicology in chapters 9 and 10 will recall that the effects of substances administered by inhalation may or may not duplicate those after absorption by other routes. In view of the considerable interest in administering the chelating agents as aerosols, a check on possible toxic effects of the DTPA-type agents on the lung was considered important. Quite naturally, much of the work was done at Pacific Northwest Laboratory. The primary investigators were V. H. Smith, J. E. Ballou, G. E. Dagle, H. A. Ragan, P. L. Hackett, and D. H. Willard.

In the 1973 annual report, it was shown that inhaled Ca-DTPA, at reasonable concentrations, produced no significant lesions in the lung except for a few emphysematous-type changes. A more complete picture was given at the IAEA seminar in 1975 (Smith et al. 1976) using rats, hamsters, and beagles. Taking the human dose equivalent as 1 g of Ca-Na₃DTPA glycinate/kg body weight, they gave from one to four human dose equivalents. The rats and hamsters developed what was referred to as a "transitory vesicular emphysema." It was not found later than three weeks after termination of the exposures.

In further Hanford studies, dogs received the agent in several doses (thirty minutes per day for five days) at an average of four times the normal human dose equivalent. There was enlargement of submucosal lymphoid follicles in the stomach and atypical cells in the alveolar lining. This was not present longer than four weeks postexposure. There is no mention of the transitory emphysema occurring in the dogs.

Since emphysema is not usually regarded as a reversible process, the PNL investigators did a repeat experiment using rats. Smith, Dagle, and Ragan (1978) gave inhalation doses equivalent to 0.4, 0.8, 1.4, and 2.2 times the dose usually administered intravenously to man. The aerosols had mass median aerodynamic diameters of 2.8 μm ($\sigma_g = 2.8$), and the maximum concentrations (2 mg Ca-DTPA/l) produced a dense fog in the aerosol chamber. Exposure periods ranged up to four hours. There was some loss of weight that was a function of dose. Blood changes were not significant. The histopathologic examination revealed no severe lesions, but there was some accumulation of histiocytes in the lung alveoli. There was also some fibrosis. A summary of the findings is given in table 19.21, taken from the 1977 annual report.

Although the lesions were in high incidence (note last column of the table), they were not severe even at the highest doses. The only incidence of concern was seen after twelve consecutive exposures. Single exposures were essentially innocuous. The incidence of emphysema was not different from that in the controls in this experiment.

The authors themselves do not draw conclusions from these data. It is apparent, however, from our review of other work that pulmonary pathology would be unlikely to take precedence over kidney, gastrointestinal tract, and other systems even on inhalation of the agents, but it cannot be disregarded.

TABLE 19.21. Incidence and Severity of Lesions in Lungs of Rats 21 and 42 Days Following Various Treatments

Lesion	Control Groups(c)			Incidence(b) in all Control Rats	Treatment Groups(c)					Incidence(b) in all DTPA Treated Rats
	Cage Controls	Cham- ber Controls	Saline Aerosol Control		Single Dose	10% Ca- DTPA	20% Ca- DTPA	40% Ca- DTPA	high Dose	
Cellular Infiltration										
No. with Lesions 21 days	10	10	10	0.95	10	10	10	10	9	0.91
42 days	8	9	10		7	9	10	6	10	
Grade(a)	(1.0)	(1.0)	(1.0)		(1.0)	(1.0)	(1.0)	(1.0)	(1.3)	
Fibrosis										
No. with Lesions 21 days	7	10	10	0.90	10	7	10	10	10	0.92
42 days	7	10	10		6	9	10	10	10	
Grade	(1.1)	(1.2)	(1.4)		(1.1)	(1.1)	(1.6)	(1.4)	(1.8)	
Histiocytosis										
No. with Lesions 21 days	0	2	1	0.05	0	2	4	5	8	0.27
42 days	0	0	0		0	1	3	3	1	
Grade	(—)	(1.0)	(1.0)		(—)	(1.0)	(1.0)	(1.1)	(1.1)	
Emphysema										
No. with Lesions 21 days	0	2	1	0.15	0	1	2	1	0	0.15
42 days	0	2	4		0	0	4	3	4	
Grade	(—)	(1.5)	(1.4)		(—)	(1.0)	(1.0)	(1.0)	(1.2)	
Foreign Body Granulomas										
No. with Lesions 21 days	0	0	0	0	0	0	0	0	0	0.02
42 days	0	0	0		0	0	0	1	1	
Grade	(—)	(—)	(—)		(—)	(—)	(—)	(2.0)	(1.0)	

(a) Average grade of lesion = lesion grades/number of rats with lesion. Lesions were ranked 1 = very slight, 2 = slight, ..., 5 = very severe. No lesions were found deserving a grade designation >2 in this study. One rat in High Dose group died but was not examined.

(b) Fraction of rats among all control or among all treated rats with lesion.

(c) See Table [3.44] for dose and treatment information.

Source: Modified from Smith, Dagle, and Ragan 1978.

The other important facet of pulmonary toxicology arises from lung lavage with the chelators. The Lovelace and Los Alamos groups have addressed this problem. The work seems to have been confined to estimating the risk of the lavage procedure itself without chelator present. We must assume that the toxicity of the chelator when administered by the lung lavage procedure is not changed from other methods.

Muggenburg et al. (1976) did risk estimates using a series of ten lung lavages in ten beagles. No changes in cardiopulmonary function were observed with moderately elaborate testing methods. There was a transient and mild reaction heard on auscultation as "scattered, moist rales" and a slight elevation of body temperature. Histologic examinations at seventy-seven days revealed evidence of low-level pneumonitis and alveolar accumulations of macrophages and other cells. The areas of damage did not show evidence that they would become permanent. Broadly, the authors conclude that multiple lung lavages carry little biomedical risk. To be on the safe side, this experiment should be repeated with

chelator present in the lavage fluid since addition of it is contemplated for human therapy in some cases.^(a)

A somewhat more cautious estimate was made by George Voeltz (the Los Alamos physician we met in connection with the plutonium workers in chapter 16) at a symposium of the Health Physics Society held in Albuquerque, New Mexico, in January 1983. Voeltz estimated the general risk of lung lavage to the average human patient as 0.2% to 0.5% for one lavage, 0.4% to 1% for two lavages, and 2% to 5% for ten lavages. This is a summation of all types of risk. While not large, these risks speak for doing whatever is possible to increase the effectiveness per lavage (see Mays et al. 1981).^(b)

7. Toxicity of Puchel

In section IV, we learned of a chelating agent, not strictly of the EDTA-DTPA type, developed in the United Kingdom that showed considerable promise for removal of recalcitrant deposits of plutonium. It was, therefore, a disappointment to find that toxicity has turned up with it. In a report by H. Smith, Stather, and Stradling (1982) of the National Radiological Protection Board (NRPB), given at a meeting of the decorporation group of the committee on internal emitters of the European Late Effects Project Group (EULEP) held at Mol, Belgium, it seemed that mice had a high LD₅₀ at one day (900 μ moles/kg or 700 mg/kg) and that surviving animals showed normal behavior, food intake, and weight gain. However, after repeated intraperitoneal injections of sodium Puchel, liver damage appeared in a few months in hamsters.

These findings prompted the NRPB people to urge more extensive toxicity studies in several species before any further consideration is given to using Puchel in humans. We can be sure that this will be done if the U.K. funding continues.

8. Miscellaneous Toxicological Findings

In addition to the entities described above, there have been reports of other toxic effects. Some of these are more or less isolated findings. Others are of only slight significance. We will list them along with the originating investigator, but without extensive comment. Many are found only in the early comprehensive review by Seven (1960).

- a. Thrombophlebitis (Seven 1960)—Since these agents were sometimes hypertonic when given, some cases of vein irritation were noted. It was recommended that they be administered at strengths no greater than 0.5% in solution in 5% glucose in water or saline.
- b. Systemic reactions (Seven 1960)—Malaise, fatigue, weakness, excessive thirst, as well as numbness, tingling, yawning, nasal congestion, and prolonged

(a) Recently, another long-term follow-up, this time of lung lavage after inhalation of ¹⁴⁴Ce, came from Lovelace (Muggenburg, McClellan, and Boecker 1981), as well as a report on removal of inhaled plutonium and americium with lung lavage and DTPA (Muggenburg, Mewhinney, and Guilmette 1981).

(b) In the 1981 discussion, Mays came up with the idea of using ultrasonic vibration to help loosen deposits of insoluble materials in the lung so that they could be removed more readily by lavage and thus reduce the risk.

sneezing; sometimes temperature elevations, have occurred in man. Hypocalcemia may be behind some of these; interference with enzymatic function in others.

- c. Histamine-like reactions (Seven 1960)—These have mostly been minor.
- d. Glycosuria (Seven 1960)—Sometimes seen in patients with Wilson's disease being treated with the chelators.
- e. Anemia (Seven 1960)—Unusual.
- f. Dermatitis (Seven 1960)—From use of disodium EDTA for prolonged periods.
- g. Hypotension (Seven 1960)—Not serious but may indicate vasodepressor activity.
- h. Embolic Phenomena (Seven 1960)—Particularly seen in vigorous treatment of patients with calcium deposits in heart valves. Since the agents are sometimes used to mobilize calcium from deposits on blood vessels, a finite chance of embolism has to exist.
- i. Interference with DNA Synthesis (several authors)—The fact that DNA synthesis can be interfered with by these chelators has been demonstrated in animals. Usually it is around the idea that zinc depletion affects the enzymes involved (Weber 1969, West Germany).
- j. Brain damage in beagle fetuses (Mays et al. 1981)—This report concerns Ca-DTPA at a dose of 30 μ moles/kg. Over half of the live-born pups died during the first week with "gross and histological evidence of brain damage" (Mays et al. 1981, p. 352). This should be followed up, especially since the dose does not seem to be high.

9. Approval of Zn-DTPA by the Food and Drug Administration

It must be noted as something of a triumph for the care and completeness of the toxicological work on these main-line chelating agents that approval has been given in the United State for clinical use of Zn-DTPA as an investigational drug for decorporation therapy of actinides. Many individuals worked hard to foster this step, which was nursed through the approval process in part by C. C. Lushbaugh (1981) and colleagues (Lushbaugh and Washburn 1979) at the Oak Ridge Institute of Nuclear Studies. The IND number is 14,603. (Special approval was given for use in Mr. McCluskey at Hanford, as described earlier.)

VII. Summary and Commentary

In the chapter on radium and later in the chapter on fallout, allusion was made to ideas and procedures for removal of or prevention of deposition of radioactive materials, especially long-lived isotopes in the body. A considerable effort went into experiments with animals and trials in humans. In the beginning, these relied primarily upon manipulations of diet or of physiological processes. Near the end of the decade of the 1940s, partly as a result of work done on complexing agents during the war, the major line of attack shifted to these. It began with attempts to solubilize heavy metal cations by such relatively normal anions as citrate. The rapid metabolism of these resulted in disappointingly short complexing periods. Next came attempts at metal displacement by other elements such as zirconium. This was promising until unexpected toxicity of zirconium in humans intervened.

British anti-lewisite (BAL), developed during the war, effectively removed or prevented the deposition of several radionuclides. However, the nuclides of

most concern, i.e., the long-retained bone-seekers, did not respond to therapy with BAL. It did work well for a soft-tissue seeker, ^{210}Po . The major avenue of attack since the early trials has been complexing by agents related to the common detergents, the so-called chelating agents (see text).

The work described in this chapter would be very incomplete if we adhered to our general policy of emphasizing studies in the United States. Therefore, the chapter is quite broad and contains summary tables of work in many countries.

Since the process of chelation is not apt to be common knowledge, a portion of the chapter is devoted to the chemistry of chelators and chelation. Substances such as EDTA (ethylenediaminetetraacetic acid) and DTPA (diethylenetriaminepentaacetic acid) are potent complexing agents for metals normally in the body as well as added metals. Thus, doses need to be carefully controlled to prevent, for example, undue removal, sequestering, or excretion of body calcium. Partly on this basis, new agents were synthesized and tried for possible increase in removal of the elements of concern (e.g., plutonium and other actinides) relative to the complexing of normal body constituents.

The experimental work with animals was extensive and is summarized in considerable detail in the chapter. There was no doubt that the chelators would work. However, they were most effective if given very soon after intake of the offending metal. Significant delay reduced effectiveness markedly. Long-term deposits, especially in bone, frequently responded hardly at all to chelators.

In addition to the animal work, there were several laboratory trials with human volunteers. These showed quite satisfactory similarities to the findings in animal experiments.

The importance of removing deposited, or about-to-be-deposited long-retained radionuclides led to many therapeutic trials in humans. Even before much of the animal work had reached reliable volume and consistency, the emergency dispensaries of large nuclear centers had chelation procedures ready and used them in several cases. In addition to the removal of systemically deposited radioactivity, much effort went into the use of chelators in the treatment of contaminated wounds.

Some of the accidental exposures and their clinical management are reviewed in the chapter. There was no doubt that the therapy could increase excretion rates. The decrease in body or organ burden was considerably less dramatic than the temporary increase in excretion rates.

Special techniques were applied to inhalation exposures. It was considered important to attempt to remove deposited radioactivity before it could be transferred to bone or sequestered in fibrotic tissue in the lungs. Thus, pulmonary lavage with various substances, including chelators, was experimented with and given at least one clinical trial for plutonium removal.

As with nearly all therapeutic modalities of considerable potency, the chelators were not without potential untoward effects. In addition to immediate reactions such as hypocalcemia, noted above, there were longer-term effects. Among these were kidney damage, pulmonary effects, and effects on the embryo and fetus. As a result, the search still continues for new and different agents. Among these are ligands of tetracatechoyl, called LICAMs, synthesized and tested at Berkeley; agents aimed at removing that portion of the radionuclide that deposits in fat (lipophilic compounds) studied at Argonne National Laboratory; attempts to improve the intracellular penetration of chelators; adjunctive therapy, studied at Los Alamos, and so-named because the agent acts as an adjunct to the chelators; and others.

In many laboratories, investigators have either persisted with or returned to more physiological methods, including manipulation of hormone balances, blocking and diluting agents, and measures to reduce gastrointestinal absorption.

On balance, it can be said that much has been learned about the metabolism, the complexing ability, the changes with time, and other parameters of deposited radionuclides from this work on therapy. Some human lives have been saved or at least materially prolonged by the therapeutic measures taken. Toxicity can be ameliorated by dividing the dose. However, no solution has been found to the need to act quickly, i.e., to get the complexing process started before the radioelement can become "fixed." As a result, clinical judgment becomes of prime importance. Frequently, physicians must decide whether or not to institute chelation therapy before they have definite answers from biopsy or bioassay samples, whole-body counting, or other means to tell them the likely dose. Thus, physicians and radiation protection experts must collaborate closely in developing early estimates of the probable deposition. Fortunately, the number of cases even approaching levels where therapy might be advised is small.

References

- Albert, A. 1979. *Selective toxicity: The physico-chemical basis of therapy*, chapter 11. London: Chapman and Hall; New York: John Wiley & Sons.
- Alderhout, J. 1972. Bio-assay results of a case of plutonium inhalation. Short communication. In *Assessment of radioactive contamination in man*, pp. 635-40. Proceedings of a symposium held in Stockholm, November 22-26; 1971. Vienna: International Atomic Energy Agency.
- Alderhout, J. and W. Hunzinger. 1971. A case of plutonium inhalation. In *Radiation protection problems relating to transuranium elements*, EUR 4612 d-f-e 259.
- Anderson, H. F., W. E. Sheehan, J. R. Mann, and R. W. Bistline. 1970. Evaluation of accidental personnel exposure to plutonium-238: Whole body counting and bioassay results. *Health Phys.* 18:631-39.
- Aposhian, H. V., R. C. Dart, M. M. Aposhian, and B. V. Dawson. 1987. Tissue decorporation of polonium-210 in rats by DMPA. *Res. Commun. Chem. Pathol. Pharmacol.* 58:157-71.
- Aposhian, H. V., H. Zheng, R. M. Maiorino, M. M. Aposhian, M. Rivera, and Q. Fernando. 1988. Unique properties of each of the water soluble dimercapto chelating agents. *The Toxicologist* 8:192. [Abstract 763 of the 27th annual meeting of the Society of Toxicology.]
- Aub, J. C. 1955. Introductory address in *Therapy of radioelement poisoning*, ed. M. W. Rosenthal, ANL-5584, pp. 2-11. Transcription of a meeting held at Argonne National Laboratory, October 1955. Argonne, Ill.: Argonne National Laboratory.
- Bair, W. J. and J. V. Dilley. 1966. *Pulmonary clearance of $^{59}\text{Fe}_2\text{O}_3$ and $^{51}\text{Cr}_2\text{O}_3$ in rats and dogs exposed to cigarette smoke*. BNWL-182. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Bair, W. J. and R. A. Hennacy. 1962. *Removing inhaled radioactive particles*. HW-72500, pp. 74-76. Richland, Wash.: Hanford Atomic Products Operations.
- Bair, W. J. and V. H. Smith. 1969. Radionuclide contamination and removal. In *Progress in nuclear energy*, ser. 12, vol. 2, *Health Physics*, pp. 157-210. Oxford-New York: Pergamon Press.
- Bair, W. J., E. G. Tombropoulos, and J. F. Park. 1963. Distribution and removal of transuranic elements and cerium deposited by the inhalation route. In *IAEA 1963*, pp. 319-38.

- Bair, W. J. and D. H. Willard. 1961. *Plutonium inhalation studies III. Effects of particle size and total dose on retention and translocation*. HW-68645. Richland, Wash.: Hanford Atomic Products Operations.
- Bair, W. J., J. E. Ballou, J. F. Park, and C. L. Sanders. 1973. Plutonium in soft tissues with emphasis on the respiratory tract. Chapter 11 in *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh, pp. 503-68. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.
- Ballou, J. E. 1962a. Preliminary evaluation of several chelating agents for plutonium removal. *Health Phys.* 8:731-34.
- Ballou, J. E. 1962b. Removal of deposited plutonium by triethylenetetramine hexaacetic acid. *Nature* 193:1303-4.
- Ballou, J. E. and J. L. Palotay. 1966. Oral therapy for deposited plutonium. *Health Phys.* 12:895-99.
- Bauer, R. O., F. R. Rullo, C. Spooner, and E. Woodman. 1952. Acute and subacute toxicity of ethylene diamine tetraacetic acid (EDTA) salts. *Fed. Proc.* 11:321.
- Baumgartner, W. V., H. V. Larson, G. H. Crook, and C. E. Newton. 1965. *The treatment and evaluation of internal deposition from a plutonium wound*. CONF. 1965-153-54. Washington, D.C.: U.S. Atomic Energy Commission.
- Baxter, D. W., M. W. Rosenthal, and A. Lindenbaum. 1973. Decorporation of monomeric plutonium from the dog by glucan and/or DTPA. *Radiat. Res.* 55:144-52.
- Baxter, D. W. and M. F. Sullivan. 1972. Gastrointestinal absorption and retention of plutonium chelates. *Health Phys.* 22:785-86.
- Belyaev, Yu. A. 1962. Effect of some complexes on plutonium removal in rats. *Plutonium-239*, Gosizdat, Moscow. FTD-TT-63-559-237, 156. Washington, D.C.: U.S. Atomic Energy Commission.
- Belyaev, Yu. A. 1965. Relative efficiency of certain complex compounds in the removal of plutonium-239 from the organism. *Radiobiology* 4(5):125-28.
- Belyaev, Yu. A. 1969. *Americium-241 distribution in rats and the effect of complexing substances on the elimination*. AEC-tr-7195, pp. 168-74. Washington, D.C.: U.S. Atomic Energy Commission.
- Bhattacharyya, M. H. and D. P. Peterson. 1979. Action of DTPA on hepatic plutonium: III. Evidence for a direct chelation mechanism for DTPA-induced excretion of monomeric plutonium into rat bile. *Radiat. Res.* 80:108-15.
- Bhattacharyya, M. H., D. P. Peterson, and A. Lindenbaum. 1978a. Action of DTPA on hepatic plutonium: I. Quantitation of the DTPA-induced biliary excretion of plutonium in the rat. *Radiat. Res.* 74:179-85.
- Bhattacharyya, M. H., D. P. Peterson, and A. Lindenbaum. 1978b. Action of DTPA on hepatic plutonium: II. DTPA-induced removal of monomeric plutonium from mouse liver parenchymal cells. *Radiat. Res.* 76:180-86.
- Boecker, B. B., B. A. Muggenburg, R. O. McClellan, S. P. Clarkson, F. J. Mares, and S. A. Benjamin. 1974. Removal of ^{144}Ce in fused clay particles from the beagle dog lung by bronchopulmonary lavage. *Health Phys.* 26:505-17.
- Bohne, F. 1972. Metabolismus und Toxizität therapeutischer Chelatbildner. XII. Mitteilung: Wirkung auf die DNS-Synthese in Kryptenzellen des Rattendarms. *Strahlentherapie* 143:106-12.
- Borisov, V. P., L. A. Ilyin, M. M. Kendysh, T. N. Shomorokhova, S. M. Mikhailovich, and L. I. Seletskaya. 1973. Mineral sorbents used as antidotes [sic] in case of radiostrontium and radiocesium intoxication. In *Health physics problems of internal contamination*, ed. E. Bujdosó, pp. 299-302. Proceedings of the 2d IRPA European congress on radiation protection. Held in Budapest, May 3-5, 1972. Budapest: Akadémiai Kiadó.
- Boss, M. R. and J. R. Mann. 1967. Body counter evaluations of plutonium exposures. *Health Phys.* 13:259-66.
- Brodsky, A., J. A. Sayeg, N. Wald, and R. Wechsler. 1968. The measurement and management of insoluble plutonium-amerium inhalation in man. In *Proceedings of the 1st international congress on radiation protection (pt. 2)*, p. 1181. Oxford, England: Pergamon Press.

- Brodsky, A., N. Wald, I. S. Horm, and B. J. Varzaly. 1969. The removal of ^{241}Am from humans by DTPA. Paper presented at the 14th annual meeting of the Health Physics Society, held in Pittsburgh, Pa.
- Brodsky, A., N. Wald, R. E. Lee, J. Horm, and R. Caldwell. 1972. Plutonium-amerium contamination aspects of a dry box involving hand amputation. In *Health Physics Operational Monitoring* 3, p. 1601. New York: Gordon & Breach.
- Bruce, R. S. 1963. Some factors influencing the absorption, retention and elimination of ruthenium. In IAEA 1963, pp. 207-24.
- Brummett, E. S. and C. W. Mays. 1977. Teratological studies of Zn-DTPA in mice. *Health Phys.* 33:624-26.
- Bulman, R. A. and R. J. Griffin. 1981. Investigations into techniques for removing intracellular plutonium—II. Complexing agents bound to macromolecules. *Health Phys.* 40:228-31.
- Calder, S. E., C. W. Mays, G. N. Taylor, and T. Brammer. 1979. Zn-DTPA safety in the mouse fetus. *Health Phys.* 36:524-26.
- Calder, S. E., G. N. Taylor, R. D. Lloyd, R. V. Petersen, D. R. Atherton, and C. W. Mays. 1978. Zn-DTPA administered by slow-release implant. *Health Phys.* 35:785-90.
- Caldwell, R. 1967. The detection of insoluble alpha emitters in the lung. CONF-661018, p. 120. Washington, D.C. U.S. Atomic Energy Commission.
- Caldwell, R. 1972. Radiological emergency experience in an industrial plant. In *Health physics operational monitoring*, vol. 3. New York: Gordon & Breach.
- Catsch, A. 1962. Principles and trends in therapeutic removal of internally deposited radionuclides. *Health Phys.* 8:725-30.
- Catsch, A. 1964. Zur toxikologie der diäthylentriaminpentaessigsäure. *Naunyn-Schmiedeberg's Arch. exp. Pathol. Pharmacol.* 246:316-29.
- Catsch, A. 1976. Removal of transuranic elements by chelating agents. Facts, open questions and prospects. In IAEA 1976, pp. 295-305.
- Catsch, A. and D. Seidl. 1963. Rare earths and ruthenium: Metabolism and removal from the mammalian body. In IAEA 1963, pp. 191-205.
- Catsch, A. and E. Von Wedelstaedt. 1965. Vergleichende untersuchungen über die Toxizität der Ca- und Zn(II)-Chelate der Diäthylentriaminpentaessigsäure. *Experimentia* 21: 210-11.
- Cohen, N. 1976. Round table discussion [at an IAEA symposium, held December 1975.] In IAEA 1976, pp. 623-24.
- Cohen, N. 1981. Chelation research at the Institute of Environmental Medicine, New York University Medical Center. In Wrenn 1981, pp. 381-82.
- Cohen, N. and R. Guilmette. 1974. Biological effects of the enhanced excretion of urinary zinc after DTPA chelation therapy. Progress report from the Institute of Environmental Medicine. COO-3382-13. New York: New York Univ.
- Cohen, N., R. A. Guilmette, and M. E. Wrenn. 1974. Chelation of ^{241}Am from the liver and skeleton of the adult baboon. *Radiat. Res.* 58:439-47.
- Cohen, N., T. Lo Sasso, and M. E. Wrenn. 1979. Metabolism of americium-241 in man: An unusual case of internal contamination of a child and his father. *Science* 206:64-66.
- Cohen, N., M. E. Wrenn, R. A. Guilmette, and T. Lo Sasso. 1976. Enhancement of ^{241}Am excretion by intravenous administration of $\text{Na}_2(\text{Ca-DTPA})$ in man and baboon—A comparison. Presented at an IAEA-WHO seminar, held December 1975. In IAEA 1976, pp. 461-75.
- Cohn, S. H. 1956. The effect of chemical agents on the skeletal content and excretion of internally deposited fission products. In *Therapy of radioelement poisoning*. ANL-5584, pp. 144-49. Transcription of a meeting held at Argonne National Laboratory, October 1955. Argonne, Ill.: Argonne National Laboratory.
- Cohn, S. H. 1963. Metabolism of fission products in man: Marshall's experience. In IAEA 1963, pp. 235-51.
- Cohn, S. H. 1982. Taped personal interview in September 1982.
- Cohn, S. H. and J. K. Gong. 1953. Effect of chemical agents on the skeletal content and excretion of injected strontium⁸⁹. *Proc. Soc. Exp. Biol. Med.* 83:550-54.

- Copp, D. H., D. J. Axelrod, and J. G. Hamilton. 1947. The deposition of radioactive metals in bone as a potential health hazard. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* 58:10-16.
- Copp, D. H., D. M. Greenberg, and J. G. Hamilton. 1946. *The deposition of plutonium and certain fission products in bone as a decontamination problem*. Metallurgical Laboratory report CH-3581, declassified document AECD-2483. Washington, D.C.: U.S. Atomic Energy Commission.
- Copp, D. H. and B. Kavin. 1956. Some considerations in fission product contamination. In *Therapy of radioelement poisoning*. ANL-5584, pp. 123-29. Transcription of a meeting held at Argonne National Laboratory, October 1955. Argonne, Ill.: Argonne National Laboratory.
- Dobson, R. L. 1956. Americium poisoning. In *Therapy of radioelement poisoning*. ANL-5584, pp. 28-35. Argonne, Ill.: Argonne National Laboratory.
- Dolphin, G. W. 1976. Review of some problems and recent research work associated with the use of chelating agents for the removal of incorporated radionuclides from humans. In IAEA 1976, pp. 403-19.
- Doull, J., C. Klaussen, and M. O. Amdur, eds. 1980. *Casarett and Doull's toxicology*. New York: Macmillan Publishing Co., Inc.
- Dudley, R. E., B. A. Muggenburg, and R. G. Cuddihy. 1978. Absorption of DTPA from the respiratory tracts of beagle dogs. In *Inhalation Toxicology Research Institute annual report 1977-78*. LF-60, pp. 195-99. Albuquerque, N. Mex.: Lovelace Biomedical and Environmental Research Foundation.
- Durbin, P. W. 1973. Metabolism and biological effects of the transplutonium elements. Part of chapter 19 in *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, J. B. Hursh, pp. 853-64. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.
- Durbin, P. W., E. S. Jones, K. N. Raymond, and F. L. Weigl. 1980. Specific sequestering agents for the actinides. IV. Removal of $^{238}\text{Pu}(4)$ from mice by sulfonated tetrameric catechyl amides. *Radiat. Res.* 81:170-87.
- Eisenbud, M. 1973. *Environmental radioactivity*, 2d ed. New York: Academic Press.
- Englehardt, S. L. 1981. The atomic man. *Reader's Digest*, April 1981, 110-14.
- Fasiska, B. C., D. E. Bohning, A. Brodsky, and J. Horm. 1971. Urinary excretion of ^{241}Am under DTPA therapy. *Health Phys.* 21:523-29.
- Federal Register*. 1978. Accidental radioactive contamination of human and animal feeds and potassium iodide as a thyroid-blocking agent in radiation emergency. *U.S. Federal Register*. December 15, 1978, pt. 7, pp. 58790-58800.
- Feldman, I. and W. F. Neuman. 1953. The uranyl-citrate system, spectrophotometric studies in acid solution. Part 1 of chapter 18, "Chemistry," in *Pharmacology and toxicology of uranium compounds*, eds. C. Voegtlin and H. C. Hodge, pp. 1087-96. National Nuclear Energy Series, div. VI, vol. 1, pt. III. New York: McGraw-Hill.
- Fisher, D. R. and B. G. Dunavant. 1978. Internal decontamination of radiocobalt. *Health Phys.* 35:279-85.
- Fisher, D. R., C. W. Mays, and G. N. Taylor. 1975. Ca-DTPA toxicity in the mouse fetus. *Health Phys.* 29:780-82.
- Foreman, H. 1950. *Chelating experiments*. Medical and Health Physics quarterly report. UCRL-960, pp. 27-32. Berkeley, Calif.: Univ. of Calif. Radiation Laboratory.
- Foreman, H. 1953. The use of chelating agents for accelerating excretion of radioelements. *J. Am. Pharm. Assoc.* 42:629-32.
- Foreman, H. 1954. *Chelating agents and stability constants*. In *Plutonium, radium, and mesothorium*, ed. C. N. Stover, pp. 258-89. Paper presented at the 2d annual conference held at the Univ. of Utah, June 17-19, 1954. Univ. of Utah: Radiobiology Laboratory.
- Foreman, H. 1955. Chelating agents. *Ind. Med. and Surg.* 24:287-92. [Prepared from a transcription of Foreman 1954.]

- Foreman, H. 1956. Clinical experiences in removal of radioelements from the body. In *Therapy of radioelement poisoning*. ANL-5584, pp. 12-23. Transcription of a meeting held at Argonne National Laboratory, October 1955. Argonne, Ill.: Argonne National Laboratory.
- Foreman, H. 1960. The pharmacology of some useful chelating agents. In *Seven and Johnson 1960*, pp. 82-94.
- Foreman, H. 1962. Toxicology: Inorganic. *Annu. Rev. pharmacol.* 2:341-62.
- Foreman, H. 1963. Medical management of radioactively contaminated wounds. In *IAEA 1963*, pp. 387-411.
- Foreman, H. and C. Finnegan. 1957. Effect of ethylenediaminetetraacetic acid on deposition and excretion of certain rare earth elements. *J. Biol. Chem.* 226:745-49.
- Foreman, H., C. Finnegan, and C. C. Lushbaugh. 1956. Nephrotoxic hazard from uncontrolled edathamil calcium-disodium therapy. *J. Am. Med. Assoc.* 160:1042-46.
- Foreman, H., P. A. Fuqua, and W. D. Norwood. 1954. Experimental administration of ethylenediamine-tetraacetic acid in plutonium poisoning. *Arch. Ind. Hyg. Occup. Med.* 10:226-31.
- Foreman, H. and V. Nigrovic. 1968. Nephrotoxicity of chelating agents. In *Diagnosis and treatment of deposited radionuclides*, eds. H. A. Kornberg and W. D. Norwood, pp. 419-23. Proceedings of the 7th annual Hanford biology symposium held in Richland, Wash., May 15-17, 1967. Amsterdam: Excerpta Medica Foundation.
- Fried, J. F. and J. Schubert. 1961. Effect of chelating agent administration on the removal of monomeric and polymeric thorium. *Radiat. Res.* 15:227-35.
- Fried, J. F., E. H. Graul, J. Schubert, and W. M. Westfall. 1959. Superior chelating agents for the treatment of plutonium poisoning. *Atompraxis* 5:1-5.
- Gemenetzs, E. 1976. *Prothrahierte Chelat-Therapie nach Inkorporation von Plutonium-239 bei der Ratte*. Thesis, Karlsruhe.
- Gensicke, F. and H. W. Nitschke. 1964. Effect of hexametaphosphate aerosols on the metabolism of inhaled ^{91}Y chloride. *Health Phys.* 10:1243-49.
- Graham, T. E. 1956. Treatment of two plutonium cases with zirconium malate in England. In *Therapy of radioelement poisoning*. ANL-5584, pp. 48-52. Transcription of a meeting held at Argonne National Laboratory, October 1955. Argonne, Ill.: Argonne National Laboratory.
- Gruner, R. and A. Seidel. 1976. Retention of ^{241}Am and ^{239}Pu in the rat as influenced by Triton WR 1339. *Health Phys.* 31:182-84.
- Guilmette, R. A. and A. Lindenbaum. 1976. Progress in the use of pyran copolymers for decorporation of polymeric plutonium. In *Health effects of plutonium and radium*, ed. W. S. S. Jee, pp. 223-31. Salt Lake City: The J. W. Press.
- Hammond, S. E. 1959. *Plutonium excretion following acute accidental exposure*. WASH-1023:84. Washington, D.C.: U.S. Atomic Energy Commission.
- Hammond, S. E., C. R. Lagerquist, and J. R. Mann. 1968. Americium and plutonium urine excretion following acute inhalation exposures to high-fired oxides. *Am. Ind. Hyg. Assoc.* 29:169-72.
- Hathaway, E. A., A. J. Finkel, J. Sedlet, and P. F. Gustafson. 1956. A thorium-227 incident. In *Therapy of radioelement poisoning*. ANL-5584, pp. 24-25. Transcription of a meeting held at Argonne National Laboratory, October 1955. Argonne, Ill.: Argonne National Laboratory.
- Heid, K. R. and J. J. Jech. 1969. Assessing the probable severity of plutonium inhalation cases. *Health Phys.* 17:433-47.
- Heid, K. R., B. D. Breitenstein, H. E. Palmer, B. J. McMurray, and N. Wald. 1979a. *The 1976 Hanford americium accident*. TID-28938. Richland, Wash.: Pacific Northwest Laboratory.
- Heid, K. R., H. E. Palmer, B. J. McMurray, B. D. Breitenstein, and N. Wald. 1979b. *The 1976 Hanford americium accident*. In *Biological implications of radionuclides released from nuclear industries*, STI/PUB/522, vol. 2, pp. 27-40. Proceedings of a symposium held in Vienna, March 26-30, 1979. Vienna: International Atomic Energy Agency.
- Hesp, R. and R. M. Ledgerwood. 1971. *The study of a case which involved a wound contaminated with plutonium and americium-241*. EUR-4612 d-f-e 273.

- Holland, J. F., E. Danielson, and A. Sahagian-Edwards. 1953. Use of ethylene diamine tetra acetic acid in hypercalcemic patients. *Proc. Soc. Exp. Biol. Med.* 84:359-64.
- Howells, H., G. B. Schofield, J. C. Lynn, and F. A. Ward. 1973. Assessment and management of a plutonium contaminated wound case. In *Health physics problems on internal contamination*, eds. E. Bujdosó, pp. 601-3. Proceedings of the 2d IRPA European congress on radiation protection held in Budapest, May 3-5, 1972. Budapest: Akadémiai Kiadó.
- Hursh, J. B. 1949. *The therapeutic use of BAL in polonium toxicity*. In three parts. UR-83, declassified 1950. Rochester, N.Y.: Univ. of Rochester.
- Hursh, J. B. 1951. The effect of BAL on the excretion and tissue distribution of polonium in rats. *J. Pharmacol. Exp. Ther.* 103:450-59.
- Hursh, J. B. 1952. Effect of BAL on survival of rats after lethal doses of polonium. *Proc. Soc. Exp. Biol. Med.* 79:210-12.
- IAEA. See International Atomic Energy Agency.
- International Atomic Energy Agency. 1963. *Diagnosis and treatment of radioactive poisoning*. Proceedings of a symposium held in Vienna, October 15-18, 1962. Vienna: World Health Organization and the International Atomic Energy Agency.
- International Atomic Energy Agency. 1976. *Diagnosis and treatment of incorporated radionuclides*, STI/PUB/411. Proceedings of an international seminar held in Vienna, December 8-12, 1975. Vienna: International Atomic Energy Agency.
- Jeanmaire, L. and J. Ballada. 1971. *Etude de deux cas de contamination par Am-241*. EUR-4612 d-f-e 531.
- Jech, J. J., B. V. Andersen, and K. R. Heid. 1972. Interpretation of human urinary excretion of plutonium for cases treated with DTPA. *Health Phys.* 22:787-92.
- Joffe, M. H. and L. A. Temple. 1953. The effect of zirconium citrate on the distribution of intravenously administered plutonium in the dog. I. Preliminary observations. In *Biology research annual report 1952*, HW-28636, pp. 92-97. Richland, Wash.: Hanford Works.
- Jolly, L., Jr., H. A. McClearen, G. A. Poda, and W. P. Walke. 1972. Treatment and evaluation of a plutonium-238 nitrate contaminated puncture wound. A two-year case history. *Health Phys.* 23:333-41.
- Jones, C. W., C. W. Mays, G. N. Taylor, R. D. Lloyd, and S. M. Packer. 1986. Reducing the cancer risk of ^{239}Pu by chelation therapy. *Radiat. Res.* 107:296-306.
- Jowsey, J. 1956. The chelation of skeletally deposited yttrium by EDTA. In *Therapy of radioelement poisoning*, ed. M. W. Rosenthal, ANL-5584, p. 130. Argonne, Ill.: Argonne National Laboratory.
- Katz, J., M. H. Weeks, and W. D. Oakley. 1954. *Relative effectiveness of various agents for preventing the internal deposition of plutonium in the rat*. HW-30437. Richland, Wash.: Hanford Works.
- Kawin, B. and D. H. Copp. 1953. Effect of 2,3-dimercaptopropanol (BAL) upon distribution and excretion of plutonium. *Proc. Soc. Exp. Biol. Med.* 84:576-77.
- Keberle, H. 1964. The biochemistry of desferrioxamine and its relation to iron metabolism. *Ann. N.Y. Acad. Sci.* 119:758-68.
- Kety, S. S. 1942. The lead citrate complex ion and its rôle in the physiology and therapy of lead poisoning. *J. Biol. Chem.* 142:181-92.
- Kisielewski, W. E., W. P. Norris, and L. A. Woodruff. 1951. The effect of BAL on distribution and metabolism of P^{32} and Sr^{90} . *Proc. Soc. Exp. Biol. Med.* 77:694-96.
- Kumatori, T. and K. Miyoshi. 1963. Clinical studies of persons injured by radioactive materials. In IAEA 1963, pp. 253-72.
- LaBelle, C. W., D. M. Bevilacqua, and H. Brieger. 1964. Synergistic effects of aerosols. IV. Therapeutic elimination of inhaled radioactive particles. *J. Occup. Med.* 6:391-95.
- LaBelle, C. W. and H. Brieger. 1960. The fate of inhaled particles in the early postexposure period. II. The role of pulmonary phagocytosis. *Arch. Environ. Health* 1:423-27.
- Lafuma, J. 1963. Diagnostic et traitement d'un cas d'intoxication par le plutonium, local d'abord et généralisé, ensuite. In IAEA 1963, pp. 381-86.
- Lagerquist, C. R., I. B. Allen, and K. L. Holman. 1967. Plutonium excretion following contaminated acid burns and prompt DTPA treatments. *Health Phys.* 13:1-4.

- Lagerquist, C. R. and S. E. Hammond. 1965. *Plutonium bioassay results following DTPA treatments on two cases 7 years after accidental exposure*. RFP-577 IV. Rocky Flats, Colo.: Dow Chemical Co.
- Lagerquist, C. R., S. E. Hammond, and D. B. Hylton. 1972. Distribution of plutonium and americium in the body 5 years after an exposure via contaminated puncture wound. *Health Phys.* 22:921-24.
- Lagerquist, C. R., E. A. Putzier, and C. W. Piltingsrud. 1967. Bio-assay and body counter results for the first 2 years following an acute plutonium exposure. *Health Phys.* 13:965-72.
- Lagerquist, C. R., S. E. Hammond, E. A. Putzier, and C. W. Piltingsrud. 1965. Effectiveness of early DTPA treatments in two types of plutonium exposures in humans. *Health Phys.* 11:1177-80.
- Larson, H. V., C. E. Newton, Jr., W. V. Baumgartner, K. R. Heid, and G. H. Crook. 1968. The management of an extensive plutonium wound and the evaluation of the residual internal deposition of plutonium. *Phys. Med. Biol.* 13:45-53.
- Laszlo, D. and H. Spencer. 1956. The interrelationship of calcium, strontium, and metal metabolism and the effect of chelating agents thereon. In *Therapy of radioelement poisoning*, ANL-5584, pp. 53-65. Transcription of a meeting held at Argonne National Laboratory, October 1955. Argonne, Ill.: Argonne National Laboratory.
- Laszlo, D. and H. Spencer. 1959. Radiostrontium metabolism and decontamination in man: Chelation in biology and medicine. In *Proceedings of the 2d United Nations international conference on the peaceful uses of atomic energy*, vol. 23, pp. 425-33. Held in Geneva, September 1-13, 1958. Geneva: United Nations. Also in *Progress in nuclear energy*, series 7, vol. 2, pp. 151-68. New York-London: Pergamon Press.
- Lindenbaum, A., M. W. Rosenthal, and R. A. Guilmette. 1976. Retention of plutonium in mouse tissues as affected by antiviral compounds and their analogs. In IAEA 1976, pp. 357-72.
- Lloyd, R. D., J. J. Boseman, G. N. Taylor, F. W. Bruenger, D. R. Atherton, W. Stevens, and C. W. Mays. 1978. Decorporation from beagles of a mixture of monomeric and particulate plutonium using Ca-DTPA and Zn-DTPA: Dependence upon frequency of administration. *Health Phys.* 35:217-27.
- Lloyd, R. D., C. W. Mays, S. S. McFarland, G. N. Taylor, and D. R. Atherton. 1976. A comparison of Ca-DTPA and Zn-DTPA for chelating ^{241}Am in beagles. *Health Phys.* 31:281-84.
- Lloyd, R. D., G. N. Taylor, J. J. Boseman, C. W. Mays, and D. R. Atherton. 1977. Further comparison of Ca-DTPA and Zn-DTPA for removal of ^{241}Am from beagles. *Health Phys.* 33:92-94.
- Lloyd, R. D., G. N. Taylor, C. W. Mays, C. W. Jones, F. W. Bruenger, and D. R. Atherton. 1979. Dependency of chelation efficacy upon time after first DTPA injection. *Radiat. Res.* 78:448-54.
- Loeffler, R. K. and J. W. Herron. 1951. *A quantitative study of percutaneous absorption V. Treatment of contaminated wounds to prevent absorption of radioactive salts*. AD-309 (B). San Francisco: Naval Radiological Defense Laboratory.
- Lushbaugh, C. C. 1981. Letter to William J. Gyrfas, U.S. Food and Drug Administration, amending IND-4041 for Ca-DTPA and IND-14603 for Zn-DTPA to permit direct intravenous injection. [Cited by Mays et al. 1981.]
- Lushbaugh, C. C. and L. C. Washburn. 1979. FDA IND approval for Zn-DTPA, new clinical agent for decorporation therapy of actinides. *Health Phys.* 36:472.
- MacDonald, N. S. 1956. Diminishing the skeletal retention of ingested radiostrontium by use of chemical agents. In *Therapy of radioelement poisoning*, ANL-5584, pp. 83-90. Transcription of a meeting held at Argonne National Laboratory, October 1955. Argonne, Ill.: Argonne National Laboratory.
- Madshus, K., A. Strömme, F. Böhne, and V. Nigrović. 1966. Diminution of radiocesium body-burden in dogs and human beings by Prussian Blue. *Int. J. Radiat. Biol. & Relat. Stud. Phys. Chem. & Med.* 10:519-20.

- Markley, J. F. 1963. Removal of polymeric plutonium from mice by combined therapy with the calcium chelate and penta-ethyl ester of DTPA. *Int. J. Radiat. Biol. & Relat. Stud. Phys. Chem. & Med.* 7:405-7.
- Markley, J. F., M. W. Rosenthal, and A. Lindenbaum. 1964. Distribution and removal of monomeric and polymeric plutonium in rats and mice. *Int. J. Radiat. Biol. & Relat. Stud. Phys. Chem. & Med.* 8:271-78.
- Máté, L., L. Varga, V. Várterész, and I. Fehér. 1973. Decorporation experiments on strontium intoxication in rats. In *Health physics problems on internal contamination*, eds. E. Bujdosó, pp. 307-11. Proceedings of the 2d IRPA European congress on radiation protection held in Budapest, May 3-5, 1972. Budapest: Akadémiai Kiadó.
- Mays, C. W., G. N. Taylor, and D. R. Fisher. 1976. Estimated toxicity of Ca-DTPA to the human fetus. *Health Phys.* 30:247-49.
- Mays, C. W., G. N. Taylor, R. D. Lloyd, and M. E. Wrenn. 1981. Status of chelation research: A review. In Wrenn 1981, pp. 351-68. [Discussion, pp. 401-4.]
- McClellan, R. O., H. A. Boyd, S. A. Benjamin, R. G. Cuddihy, F. F. Hahn, R. K. Jones, J. L. Mauderly, J. A. Mewhinney, B. A. Muggenburg, and R. C. Pfleger. 1972a. Bronchopulmonary lavage and DTPA treatment of an accidental inhalation ^{239}Pu exposure case. In *Fission Product Inhalation Project annual report 1971-72*, LF-45, pp. 287-94. Albuquerque, N. Mex.: Inhalation Toxicology Research Institute, Lovelace Biomedical and Environmental Research Institute.
- McClellan, R. O., H. A. Boyd, S. A. Benjamin, R. G. Cuddihy, F. F. Hahn, R. K. Jones, J. L. Mauderly, J. A. Mewhinney, B. A. Muggenburg, and R. C. Pfleger. 1972b. Recovery of ^{239}Pu following bronchopulmonary lavage and DTPA treatment of an accidental inhalation exposure case. *Health Phys.* 23:426 (Abstract P/102).
- McClinton, L. T. and J. Schubert. 1948. The toxicity of some zirconium and thorium salts in rats. *J. Pharmacol. Exp. Ther.* 94:1-6.
- Metivier, H., D. Nolibé, R. Masse, and J. Lafuma. 1974. Excretion and acute toxicity of $^{239}\text{PuO}_2$ in baboons. *Health Phys.* 27:512-14.
- Michon, G. 1956. Décontamination radioactive cutanée par ionophorèse. *C. R. Hebd. Séances Acad. Sci.* 243:976-78.
- Morgan, R. M. and H. Smith. 1974a. Histological changes in kidney, liver and duodenum of the mouse following the acute and subacute administration of diethylenetriaminepentaacetic acid. *Toxicology* 2:153-63.
- Morgan, R. M. and H. Smith. 1974b. The effect of acute and sub-acute treatment with diethylenetriaminepentaacetic acid on the hepatic function of mice. *Toxicology* 2:43-49.
- Morin, M., J. C. Nénot, and J. Lafuma. 1972. Metabolic and therapeutic study following administration to rats of ^{238}Pu nitrate: A comparison with ^{239}Pu . *Health Phys.* 23:475-80.
- Morin, M., J. C. Nénot, and J. Lafuma. 1974. Distribution and removal by DTPA of injected ^{252}Cf in the Rat. *Health Phys.* 26:323-26.
- Muggenburg, B. A., S. A. Felicetti, and S. A. Silbaugh. 1977. Removal of inhaled radioactive particles by lung lavage—A review. *Health Phys.* 33:213-20.
- Muggenburg, B. A. and J. L. Mauderly. 1975. Lung lavage using a single-lumen endotracheal tube. *J. Appl. Physiol.* 38:922-26.
- Muggenburg, B. A., J. A. Mewhinney, and R. A. Guilmette. 1981. Removal of inhaled plutonium and americium from dogs using lung lavage and DTPA. In Wrenn 1981, pp. 387-93.
- Muggenburg, B. A., A. F. Eidson, J. A. Mewhinney, and R. A. Guilmette. 1979. Removal of inhaled mixed oxide particles of uranium and plutonium from beagle dogs using combined lung lavage and DTPA treatment. In *Inhalation Toxicology Research Institute annual report 1978-79*, LF-69, pp. 195-98. Albuquerque, N. Mex.: Lovelace Biomedical and Environmental Research Institute.
- Muggenburg, B. A., J. L. Mauderly, D. O. Slauson, and W. H. Halliwell. 1976. Biomedical risks of multiple lung lavages in beagle dogs. In *Inhalation Toxicology Research Institute annual report 1975-76*, LF-56, pp. 418-22. Albuquerque, N. Mex.: Lovelace Biomedical and Environmental Research Institute.

- Muggenburg, B. A., R. O. McClellan, B. B. Boecker, J. L. Mauderly, and F. F. Hahn. 1981. Long-term biologic effects in dogs treated with lung lavage after inhalation of ^{144}Ce in fused aluminosilicate particles. In Wrenn 1981, pp. 395-400.
- Muggenburg, B. A., R. C. Pflieger, R. G. Cuddihy, and R. O. McClellan. 1972. The removal of inhaled $^{144}\text{CeCl}_3$ from beagle dogs. III. Bilateral-bronchopulmonary lavage with a DTPA solution. *Health Phys.* 23:611-19.
- National Council on Radiation Protection and Measurements. 1977. *Protection of the thyroid gland in the event of releases of radioiodine*. NCRP report no. 55. Bethesda, Md.
- National Council on Radiation Protection and Measurements. 1980. *Management of persons accidentally contaminated with radionuclides*. NCRP report no. 65. Bethesda, Md.
- NCRP. See National Council on Radiation Protection and Measurements.
- Neef, N. I. and J. E. Ballou. 1957. *Ultrasonic methods of decontaminating rat skin contaminated with yttrium-91 and plutonium-239*. HW-51939. Richland, Wash.: Hanford Atomic Products Operation.
- Nelson, A. 1963. Attempts to influence the uptake, retention and excretion of radiostrontium in animals, in IAEA 1963, pp. 95-117.
- Nénot, J. C., M. Morin, and J. Lafuma. 1970. Étude expérimentale des contaminations par le curium-242 et de leur traitement. *Health Phys.* 18:613-22.
- Nénot, J. C., M. Morin, and J. Lafuma. 1971a. Contaminations expérimentales par l'américium en solution et leur traitement. *Health Phys.* 20:383-91.
- Nénot, J. C., M. Morin, and J. Lafuma. 1971b. Étude expérimentale de la décontamination du squelette après inhalation de nitrate d'américium. *Health Phys.* 21:395-400.
- Nénot, J. C., M. Morin, W. Skupinski, and J. Lafuma. 1972. Experimental removal of ^{144}Ce , ^{241}Am , ^{242}Cm , and ^{238}Pu from the rat skeleton. *Health Phys.* 23:635-40.
- Neuman, W. F. and R. P. Allen. 1949. The failure of 2,3 dithiopropionol (BAL) to affect acute, systemic uranium poisoning. *J. Pharmacol. Exp. Ther.* 96:95-98.
- Nolibé, D., H. Metivier, R. Masse, and J. Lafuma. 1977. Therapeutic effect of pulmonary lavage *in vivo* after inhalation of insoluble radioactive particles. In *Inhaled particles IV*, Part 2, ed. W. H. Walton, pp. 597-613. Proceedings of an international symposium held in Edinburgh, September 22-26, 1975. Oxford-New York: Pergamon Press.
- Nordenström-Blomqvist, B. E. W. 1950. An attempt of excreting injected Thorotrast in rabbits by 2,3-dimercaptopropanol (BAL). *Acta Radiol.* 34:533-45.
- Norwood, W. D. 1956. Treatment of plutonium poisoning with zirconium citrate and with CaEDTA. In *Therapy of radioelement poisoning*, ANL-5584, pp. 36-44. Transcription of a meeting held at Argonne National Laboratory, October 1955. Argonne, Ill.: Argonne National Laboratory.
- Norwood, W. D. 1960a. Diethylenetetraminepentaacetic acid effectiveness in removing internally deposited plutonium from humans. *J. Occup. Med.* 2:371-76.
- Norwood, W. D. 1960b. Treatment of plutonium deposition in humans with DTPA—effectiveness of long-term administration and oral administration. In *Proceedings of the 13th international congress on occupational health*, pp. 335-38. New York.
- Norwood, W. D. 1962a. Long-term administration of DTPA for plutonium elimination. A follow-up study in one patient. *J. Occup. Med.* 4:130-32.
- Norwood, W. D. 1962b. Therapeutic removal of plutonium in humans. *Health Phys.* 8:747-50.
- Norwood, W. D. 1963. Removal of plutonium and other transuranic elements from man. In IAEA 1963, pp. 307-18.
- Norwood, W. D., P. A. Fuqua, R. H. Wilson, and J. W. Healy. 1959. Treatment of plutonium inhalation: Case studies. In *Proceedings of the 2d United Nations international conference on the peaceful uses of atomic energy*, vol. 23, pp. 434-38. Held in Geneva, September 1-13, 1958. Geneva: United Nations. Also in *Progress in nuclear energy*, vol. 2, pp. 105-13. New York-London: Pergamon Press.
- Ohlenschläger, L. 1971. Bericht über eine mit Americium-241 kontaminierte Stich-Schnittverletzung am linken Zeigefinger. *Strahlentherapie* 142:73-79.
- Ohlenschläger, L. 1976. Efficacy of Zn-DTPA in removing plutonium from the human body. *Health Phys.* 30:249-50.

- Ohlenschläger, L. and H. Schieferdecker. 1973. Bericht über eine mit Plutonium 239 kontaminierte Riss-Schnittverletzung. *Strahlentherapie* 146:675-84.
- Ohlenschläger, L. and H. Schieferdecker. 1976. Comparison of results of drug therapy of ^{239}Pu incorporation after wound contamination. In IAEA 1976, pp. 491-96.
- Painter, E., E. Russell, C. L. Prosser, M. N. Swift, W. Kisielleski, and G. Sacher. 1946. *Clinical physiology of dogs injected with plutonium*. Metallurgical Laboratory report CH-3858, issued June 1946, declassified June 1948 as AECD-2042. Washington, D.C.: U.S. Atomic Energy Commission.
- Palmer, H. E. and I. C. Nelson. 1970. The uptake, distribution and excretion of promethium in humans and the effect of DTPA on these parameters. *Health Phys.* 18:53-61.
- Parker, H. G., A. de G. Low-Beer, and E. L. Isaac. 1962. Comparison of retention and organ distribution of Am^{241} and Cf^{252} in mice: The effect of *in vivo* DTPA chelation. *Health Phys.* 8:679-84.
- Parker, H. G., S. R. Wright, A. De G. Low-Beer, and D. J. Yaeger. 1972. The metabolism of ^{253}Es in mice. *Health Phys.* 22:647-51.
- Parker, H. M. 1973. Plutonium. Industrial hygiene, health physics and related aspects. Chapter 14 in *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh, pp. 613-67. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.
- Peters, R. A., L. A. Stocken, and R. H. S. Thompson. 1945. British anti-lewisite (BAL). *Nature* 156:616-19.
- Pfleger, R. C., A. J. Wilson, and R. O. McClellan. 1969. Pulmonary lavage as a therapeutic measure for removing inhaled "Insoluble" materials from the lung. *Health Phys.* 16:758-63.
- Pfleger, R. C., B. A. Muggenburg, R. G. Cuddihy, and R. O. McClellan. 1972a. The removal of inhaled $^{144}\text{CeCl}_3$ from beagle dogs. II. Intravenous administration of a DTPA solution. *Health Phys.* 23:605-9.
- Pfleger, R. C., B. A. Muggenburg, D. H. Sesline, J. W. Harvey, R. G. Cuddihy, and R. O. McClellan. 1972b. The removal of inhaled $^{144}\text{CeCl}_3$ from beagle dogs. I. Unilateral bronchopulmonary lavage with a DTPA solution. *Health Phys.* 23:595-603.
- Pfleger, R. C., A. J. Wilson, R. G. Cuddihy, and R. O. McClellan. 1969. Bronchopulmonary lavage for removal of inhaled insoluble materials from the lung. *Diseases of the Chest* 56:524-30.
- Piltingsrud, C. W. 1964. *Treatment of plutonium contaminated wounds*. RFP-381. Rocky Flats, Colo.: Dow Chemical Company.
- Planas-Bohne, F. and H. Ebel. 1975. Dependence of DTPA-toxicity on the treatment schedule. *Health Phys.* 29:103-6.
- Planas-Bohne, F. and J. Lohbreier. 1976. Toxicological studies on DTPA. In IAEA 1976, pp. 505-15.
- Plotnikova, L. A. and G. D. Baisogolov. 1964. The effect of $\text{Na}_3\text{Ca-DTPA}$ (pentacine) on the excretion of Pu^{239} from the human organism. *Med. Radiol.* 9:49-52.
- Polig, E. 1976a. The influence of ^{241}Am and DTPA on morphometric parameters of the rat femur. *Radiat. and Environ. Biophys.* 13:27-41.
- Polig, E. 1976b. Topographic analysis of the microdistribution of ^{241}Am in the rat femur as influenced by DTPA treatment. *Radiat. Res.* 67:128-141.
- Putzier, E. A., C. R. Lagerquist, S. E. Hammond, J. R. Mann, and C. W. Piltingsrud. 1965. *Evaluation and treatment of an acute internal exposure to plutonium*. RFP-446. Rocky Flats, Colo.: Dow Chemical Company.
- Rahman, Y.-E., M. W. Rosenthal, and E. A. Cerny. 1973. Intracellular plutonium: Removal by liposome-encapsulated chelating agent. *Science* 180:300-302.
- Raymond, K. N. and W. L. Smith. 1981. Actinide specific sequestering agents and decontamination applications. In *Structure and bonding*, eds. J. B. Goodenough et al., vol. 43, pp. 159-86. New York-Berlin: Springer-Verlag.
- Richmond, C. R., G. A. Drake, and J. E. London. 1973. Enhanced removal of radio-rubidium from rodents and beagles with ferric ferrocyanide. *Radiat. Res.* 55:546-47 [abstract].

- Richmond, C. R. and J. E. Furchner. 1961. Effect of a carbonic anhydrase inhibitor (Diamox) on Cs^{137} excretion by rats. *Health Phys.* 6:36-40.
- Rosen, J. C., D. Gur, S. F. Pan, and N. Wald. 1980. Long-term removal of ^{241}Am using Ca-DTPA. *Health Phys.* 39:601-9.
- Rosenthal, M. W. 1956. The use of zirconium and other carriers in the removal of radioelements from the body: Comments on the use of complexing agents. In *Therapy of radioelement poisoning*, ANL-5584, pp. 100-113. Transcription of a meeting held at Argonne National Laboratory, October 1955. Argonne, Ill.: Argonne National Laboratory.
- Rosenthal, M. W. and A. Lindenbaum. 1964. Effects of desferrioxamine B-methane sulfonate (DFOM) on removal of plutonium *in vitro* and *in vivo*. *Proc. Soc. Exp. Biol. Med.* 117:749-50.
- Rosenthal, M. W. and A. Lindenbaum. 1967. Influence of DTPA therapy on long-term effects of retained monomeric plutonium: Comparison with polymeric plutonium. *Radiat. Res.* 31:506-21.
- Rosenthal, M. W., M. Smoler, and A. Lindenbaum. 1968. Combined reticuloendothelial stimulation and long-term, intermittent DTPA therapy in poisoning by polymeric plutonium. In *Diagnosis and treatment of deposited radionuclides*, eds. H. A. Kornberg and W. D. Norwood, pp. 403-12. Proceedings of the 7th annual Hanford biology symposium held in Richland, Wash., May 15-17, 1967. Amsterdam: Excerpta Medica Foundation.
- Rosenthal, M. W., H. Brown, D. L. Chladek, E. S. Moretti, J. J. Russell, and A. Lindenbaum. 1973. Removal of plutonium from mouse liver by glucan and DTPA. *Radiat. Res.* 53:102-14.
- Rosenthal, M. W., Y. E. Rahman, E. S. Moretti, and E. A. Cerny. 1975. Removal of polymeric plutonium by DTPA directed into cells by liposome encapsulation. *Radiat. Res.* 63:262-74.
- Rosenthal, M. W., J. J. Russell, E. S. Moretti, and A. Lindenbaum. 1969. Effective dose of DTPA, spaced at 3 day intervals, in removal of skeletal plutonium. *Health Phys.* 16:806-8.
- Rosoff, B., S. Ritter, K. Sullivan, H. Hart, and H. Spencer-Laszlo. 1961. Effect of chelating agents on the removal of yttrium and lanthanum from man. *Health Phys.* 6:177-82.
- Sanders, C. L. 1969. Factors influencing the removal of inhaled $^{239}\text{PuO}_2$ particles by pulmonary washing. *Toxicol. Appl. Pharmacol.* 14:637 [abstract].
- Sanders, C. L. and R. R. Adee. 1968. Phagocytosis of inhaled plutonium oxide— ^{239}Pu particles by pulmonary macrophages. *Science* 162:918-20.
- Sanders, C. L. and D. M. Meier. 1973. Effects of DTPA on excretion and tissue distribution of injected ^{239}Pu in fed and fasting rats. *Health Phys.* 25:405-11.
- Sanders, S. M., Jr. 1961. Plutonium excretion. Study following treatment with zirconium citrate and Edathamil calcium-disodium. *Arch. Environ. Health* 2:474-83.
- Sanders, S. M., Jr. 1974. Excretion of ^{241}Am and ^{244}Cm following two cases of accidental inhalation. *Health Phys.* 27:359-65.
- Schmidtke, I. 1964. Removal of inhaled radioactive yttrium by the use of diethylene-triamine-pentaacetic acid (DTPA). *Health Phys.* 10:1235-41.
- Schofield, G. B. 1969. Comparisons in the medical management of three cases of plutonium-contaminated wounds. In *Handling of radiation accidents*, STI/PUB/229, pp. 163-72. Proceedings of a symposium held in Vienna, May 19-23, 1969. Vienna: International Atomic Energy Agency.
- Schofield, G. B. and J. C. Lynn. 1973. A measure of the effectiveness of DTPA chelation therapy in cases of plutonium inhalation and plutonium wounds. EUR-4612 d-f-e 273. *Health Phys.* 24:317-26.
- Schofield, G. B., H. Howells, F. Ward, J. C. Lynn, and G. W. Dolphin. 1974. Assessment and management of a plutonium contaminated wound case. *Health Phys.* 26:541-54.
- Schroeder, H. A. 1960. Discussion section (Chapter 18) led by Dr. Schroeder. In *Seven and Johnson 1960*, pp. 154-59.

- Schubert, J. 1945. Complexes between fission products, product and uranium with organic compounds of biological importance and a simple rapid method for the determination of their composition and dissociation constants. Metallurgical Laboratory memorandum to W. E. Cohn, February 3, 1945.
- Schubert, J. 1947. Treatment of plutonium poisoning by metal displacement. *Science* 105:389-90.
- Schubert, J. 1949. An experimental study of the effect of zirconium and sodium citrate treatment on the metabolism of plutonium and radioyttrium. *J. Lab. Clin. Med.* 34:313-25.
- Schubert, J. 1954. Discussion of paper by Dr. Harry Foreman. In *Proceedings of the 2d annual conference on plutonium, radium, and mesothorium*, ed. C. N. Stover, Jr., pp. 289-99. Held June 17-19, 1954. Salt Lake City: Univ. of Utah, Radiobiology Laboratory.
- Schubert, J. 1979. Mixed ligand chelate therapy for plutonium and cadmium poisoning. *Nature* 281:406.
- Schubert, J. 1980. Reply to Dr. Volf. *Health Phys.* 39:585.
- Schubert, J. and S. K. Derr. 1978. Mixed ligand chelate therapy for plutonium and cadmium poisoning. *Nature* 275:311-13.
- Schubert, J. and M. R. White. 1950a. Effect of citrate salts and other chemical factors on the distribution and excretion of beryllium. *J. Lab. Clin. Med.* 35:854-64.
- Schubert, J. and M. R. White. 1950b. The effect of different dose levels of zirconium on the excretion and distribution of plutonium and yttrium. *J. Biol. Chem.* 184:191-96.
- Schubert, J., J. F. Fried, M. W. Rosenthal, and A. Lindenbaum. 1961. Tissue distribution of monomeric and polymeric plutonium as modified by a chelating agent. *Radiat. Res.* 15:220-26.
- Schulte, H. F. and H. O. Whipple. 1968. Chelating agents in plutonium deposition—A minority view. In *Diagnosis and treatment of deposited radionuclides*, eds. H. A. Kornberg and W. D. Norwood, pp. 587-92. Proceedings of the 7th annual Hanford biology symposium held in Richland, Wash., May 15-17, 1967. Amsterdam: Excerpta Medica Foundation.
- Seidel, A. 1975. Removal from the rat of internally deposited ^{241}Am by long-term treatment with Ca- and Zn-DTPA. *Radiat. Res.* 61:478-87.
- Seidel, A. 1976. Removal of ^{252}Cf and ^{241}Am from the rat by means of Ca-DTPA and Zn-DTPA. In IAEA 1976, pp. 323-39.
- Seidel, A. 1977. Decorporation of ^{241}Am and ^{252}Cf by CaDTPA from rat, Syrian and Chinese hamster. In *Recueil des communications—Proceedings*, vol. 4, pp. 1177-80. Proceedings of the 4th international congress of the IRPA held in Paris, April 24-30, 1977. Paris: International Radiation Protection Association.
- Seidel, A. and V. Volf. 1972. Removal of internally deposited transuranium elements by Zn-DTPA. *Health Phys.* 22:779-83.
- Seidel, A. and V. Volf. 1975. Experimental decorporation of radionuclides: Basic methodology. In *Problems and methodology of experimental evaluation of biological effects of radionuclides*. Brussels, Belgium: EULEP.
- Seven, M. J. 1960. Observations on the toxicity of intravenous chelating agents. Chapter 10 in Seven and Johnson 1960.
- Seven, M. J. and L. A. Johnson, eds. 1960. *Metal binding in medicine*. Proceedings of a symposium held at Hahnemann Medical College, Philadelphia, May 1959. Philadelphia, Pa.: J. B. Lippincott.
- Severa, J. 1973. Zirconium compounds in the therapy of internal contamination. In *Health physics problems on internal contamination*, eds. E. Bujdosó, pp. 327-30. Proceedings of the 2d IRPA European congress on radiation protection held in Budapest, May 3-5, 1972. Budapest: Akadémiai Kiadó.
- Sikov, M. R., V. H. Smith, and D. D. Mahlum. 1975. Teratological effectiveness and fetal toxicity of DTPA in the rat. *Pacific Northwest Laboratory annual report for 1974 to the ERDA Division of Biomedical and Environmental Research, Part 1 Biomedical sciences*. BNWL-1950, pt. 1, pp. 138-40. Richland, Wash.: Battelle, Pacific Northwest Laboratories.

- Silbaugh, S. A., S. A. Felicetti, B. A. Muggenburg, and B. B. Boecker. 1975. Multiple bronchopulmonary lavages for the removal of ^{144}Ce in fused clay particles from beagle dog lungs. *Health Phys.* 29:81-88.
- Smith, H., J. W. Stather, and G. N. Stradling. 1982. Toxicological data on PUCHEL. In *Newsletter of European Late Effects Project Group*, Newsletter 30, September 1982, pp. 25-27.
- Smith, V. H. 1958. Removal of internally deposited plutonium. *Nature* 181:1792-93.
- Smith, V. H. 1963. *Prevention of plutonium and neptunium deposition*. HW-7600, p. 143. Richland, Wash.: Hanford Works.
- Smith, V. H. 1964. Prevention of plutonium deposition by desferrioxamine-B. *Nature* 204:899-900.
- Smith, V. H. 1965. Removal of internally deposited ruthenium from rats. In *Hanford biology research annual report for 1964*. BNWL-122, pp. 122-24. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Smith, V. H. 1970a. Effect of age on plutonium removal. In *Pacific Northwest Laboratory annual report for 1969 to the USAEC Division of Biology and Medicine, Vol. 1 Life sciences, Part 1 Biomedical sciences*. BNWL-1306, pt. 1, pp. 69-70. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Smith, V. H. 1970b. Effect of promethium concentration on deposition and removal in the rat. In *Pacific Northwest Laboratory annual report for 1968 to the USAEC Division of Biology and Medicine, Vol. 1 Life sciences, Part 1 Biomedical sciences*. BNWL-1050, pp. 5.5-5.8. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Smith, V. H. 1970c. Promethium removal studies in miniature swine. In *Pacific Northwest Laboratory annual report for 1968 to the USAEC Division of Biology and Medicine, Vol. 1 Life sciences, Part 1 Biomedical sciences*. BNWL-1050, pt. 1, pp. 5.8-5.10. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Smith, V. H. 1970d. Removal of firmly bound promethium from the rat. In *Pacific Northwest Laboratory annual report for 1968 to the USAEC Division of Biology and Medicine, Vol. 1 Life sciences, Part 1 Biomedical sciences*. BNWL-1050, pt. 1, pp. 5.3-5.4. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Smith, V. H. 1972a. Interaction of plutonium and cerium during chelation therapy in rats. In *Pacific Northwest Laboratory annual report for 1971 to the USAEC Division of Biology and Medicine, Vol. 1 Life sciences, Part 1 Biomedical sciences*. BNWL-1650, pt. 1, pp. 274-76. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Smith, V. H. 1972b. Therapeutic removal of internally deposited transuranium elements. *Health Phys.* 22:765-78.
- Smith, V. H. 1979. Taped personal interview in June 1979.
- Smith, V. H. 1981. Therapy for incorporated radionuclides: Scope and need. In Wrenn 1981, pp. 345-49.
- Smith, V. H., G. E. Dagle, and H. A. Ragan. 1978. Acute toxicity of inhaled Ca-DTPA to the rat lung. In *Pacific Northwest Laboratory annual report for 1977 to the DOE Assistant Secretary for Environment, Part 1 Biomedical sciences*. PNL-2500, pt. 1, pp. 3.103-3.105. Richland, Wash.: Pacific Northwest Laboratory.
- Smith, V. H. and M. F. Sullivan. 1978. Removal of plutonium from the neonatal rat. In *Pacific Northwest Laboratory annual report for 1977 to the DOE Assistant Secretary for Environment, Part 1 Biomedical sciences*. PNL-2500, pt. 1, pp. 3.107-3.109. Richland, Wash.: Pacific Northwest Laboratory.
- Smith, V. H., J. E. Ballou, W. J. Clarke, and R. C. Thompson. 1961. Effectiveness of DTPA in removing plutonium from the pig. *Proc. Soc. Exp. Biol. Med.* 107:120-23.
- Smith, V. H., J. E. Ballou, J. E. Lund, G. E. Dagle, H. A. Ragan, R. H. Busch, P. L. Hackett, and D. W. Willard. 1976. Aspects of inhaled DTPA toxicity in rat, hamster, and beagle dog and treatment effectiveness for excorporation of plutonium from the rat. In *IAEA 1976*, p. 517.
- Sowby, F. D. and D. M. Taylor. 1960. Removal of internally deposited americium by chelating agents. *Nature*. 187:612.
- Spencer, H. 1963. Removal of radiostrontium from man. In *IAEA 1963*, pp. 145-55.

- Spencer, H., L. Kramer, and J. Samachson. 1972. Metabolism and removal of radiostrontium in man. In *Biomedical implications of radiostrontium exposure*, eds. M. Goldman and L. K. Bustad, CONF-710201, pp. 31-51. Proceedings of a symposium held in Davis, Calif., February 22-24, 1971. AEC symposium series 25. Springfield, Va.: National Technical Information Service.
- Spencer, H. and D. Laszlo. 1960. Removal of radiostrontium in man. In *Seven and Johnson 1960*, pp. 169-78.
- Spencer, H. and B. Rosoff. 1963. Metabolism and removal of rare earths in man. In *IAEA 1963*, pp. 171-89.
- Spencer, H. and B. Rosoff. 1965. Removal of scandium-46 in man. *Health Phys.* 11: 1181-85.
- Spencer, H. and B. Rosoff. 1966. Effect of chelating agents on the removal of zinc-65 in man. *Health Phys.* 12:475-80.
- Spencer, H., J. Samachson, E. P. Hardy, Jr., and J. Rivera. 1965. Effect of intravenous calcium and of orally administered ammonium chloride on strontium-90 excretion in man. *Radiat. Res.* 25:695-705.
- Stannard, J. N. and H. Haydon. 1956. *The effect of BAL (British anti-lewisite) on distribution and excretion of orally administered polonium-210*. UR-429. Rochester, N.Y.: Univ. of Rochester.
- Stara, J. F. and D. Waldron-Edward. 1968. Repressive action of sodium alginate on absorption of radioactive strontium and calcium in cats. In *Diagnosis and treatment of deposited radionuclides*, eds. H. A. Kornberg and W. D. Norwood, pp. 340-54. Proceedings of the 7th annual Hanford biology symposium held in Richland, Wash., May 15-17, 1967. Amsterdam: Excerpta Medica Foundation.
- Stather, J. W., H. Smith, A. C. James, and P. Rodwell. 1976. The experimental use of aerosol and liposomal forms of Ca-DTPA as a treatment for plutonium contamination. In *IAEA 1976*, p. 387.
- Stevens, W., D. R. Atherton, B. J. Grube, and F. W. Bruenger. 1974. Alternate methods for administering chelating agents in decorporation therapy. In *Research in Radiobiology annual report of work in progress in the Internal Irradiation Program*, COO-119-249, pp. 149-160. Salt Lake City: Univ. of Utah, Radiobiology Laboratory.
- Stover, B. J., A. G. Ruhmann, and D. R. Atherton. 1966. The action of chelating agents on the ^{212}Pb in the blood: The particular value of the steady state after ^{228}Th administration to the beagle. *Int. J. Radiat. Biol. & Relat. Stud. Phys. Chem. & Med.* 11:27-34.
- Stover, B. J., D. R. Atherton, E. F. Holt, and D. S. Buster. 1958. *Effect of DTPA on the excretion of Th^{228} daughters*. COO-215, pp. 127-32. Salt Lake City: Univ. of Utah, Radiobiology Laboratory.
- Stradling, G. N. and R. A. Bulman. 1981. Recent research on decorporation therapy at National Radiological Protection Board. In *Wrenn 1981*, pp. 369-79.
- Swanberg, F., Jr. and R. C. Henje. 1964. Excretion of ^{239}Pu in a patient with a plutonium-contaminated injury. *J. Occup. Med.* 6:174-78.
- Takada, K. and V. Volf. 1977. Comparison of the effectiveness of CaDTPA and ZnDTPA in removing ^{242}Cm from the rat. *Radiat. Res.* 70:164-72.
- Taylor, D. M. 1967. The effects of desferrioxamine on the retention of actinide elements in the rat. *Health Phys.* 13:135-40.
- Taylor, D. M., A. R. Chipperfield, and A. C. James. 1971. The effects of tetracycline on the deposition of plutonium and related elements, in rat bone. *Health Phys.* 21:197-204.
- Taylor, D. M. and J. D. Jones. 1972. Effects of ethylenediaminetetraacetate and diethylenetriaminepentaacetate of DNA. Synthesis in kidney and intestinal mucosa of folate treated rats. *Biochem. Pharmacol.* 21:3313-15.
- Taylor, D. M. and F. D. Sowby. 1962. The removal of americium and plutonium from the rat by chelating agents. *Phys. Med. Biol.* 7:83-91.
- Taylor, D. M. and V. Volf. 1980. Oral chelation treatment of injected ^{241}Am or ^{239}Pu in rats. *Health Phys.* 38:147-58.
- Taylor, G. N. and C. W. Mays. 1978. Fetal injury induced by Ca-DTPA in dogs. *Health Phys.* 35:858-60.

- Taylor, G. N., R. D. Lloyd, J. J. Boseman, D. R. Atherton, and C. W. Mays. 1978. Removal of plutonium from beagles using Ca-DTPA and Zn-DTPA: Effects of initial DTPA injection. *Health Phys.* 35:201-10.
- Taylor, G. N., J. L. Williams, L. Roberts, D. R. Atherton, and L. Shabestari. 1974. Increased toxicity of Na_2CaDTP when given by protracted administration. *Health Phys.* 27:285-88.
- Testa, C. and A. Delle Site. 1973. The study of a case which involved a wound contaminated with insoluble Pu and ^{241}Am . In *Health physics problems of internal contamination*, ed. E. Bujdosó, pp. 593-99. Proceedings of the 2d IRPA European congress on radiation protection held in Budapest, May 3-5, 1972. Budapest: Akadémiai Kiadó.
- Thomas, R. G. and T. L. Chiffelle. 1974. Experimental alteration of rat lung clearance patterns by zymosan injection. *J. Reticuloendothel. Soc.* 15:48-60.
- Thomas, R. C., J. K. Scott, and R. L. Thomas. 1969. Effect of injected zymosan on inhalation of particulates. *J. Reticuloendothel. Soc.* 6:606-22.
- Thompson, R. C. 1956. Research at Hanford on therapy of internally deposited plutonium. In *Therapy of radioelement poisoning*, ANL-5584, pp. 114-22. Transcription of a meeting held at Argonne National Laboratory, October 1955. Argonne, Ill.: Argonne National Laboratory.
- Thompson, R. C. 1967. Biological factors. Chapter 23 in *Plutonium handbook, a guide to the technology*, ed. O. J. Wick, vol. 2, pp. 785-829. New York: Gordon & Breach.
- Thompson, R. C., ed. 1983. 1976 Hanford americium exposure incident. *Health Phys.* 45:837-947 [special issue].
- Tombropoulos, E. G. 1964. Review of therapeutic procedures for removal of inhaled radioactive materials. *Health Phys.* 10:1251-57.
- Tombropoulos, E. G. and W. J. Bair. 1962. Treatment for removal of inhaled radioactive ceria ($^{144}\text{CeO}_2$) from the lungs of rats. *Nature* 196:82-83.
- Tombropoulos, E. G., W. J. Bair, and J. F. Park. 1963. Effect of diethylenetriamine-pentaacetic acid and polypropyleneglycolethylene oxide polymer on excretion of inhaled $^{239}\text{PuO}_2$ in dogs. *Nature* 198:703-4.
- Tombropoulos, E. G., W. J. Bair, and J. F. Park. 1969. Removal of inhaled ^{144}Ce - ^{144}Pr oxide by diethylenetriaminepentaacetic acid (DTPA) treatment. I: ^{144}Ce - ^{144}Pr oxide prepared by peroxide oxidation. *Health Phys.* 16:333-38.
- Tombropoulos, E. G., C. E. Breckinridge, W. J. Bair, and N. E. McDonald. 1964. Attempts to remove inhaled plutonium. HW-80500, pp. 44-46. Richland, Wash.: Hanford Atomic Products Operation.
- Vanderborght, O. L. J., S. Van Puymbroeck, and I. Babakova. 1978. Effect of combined alginate treatments on the distribution and excretion of an old radiostrontium contamination. *Health Phys.* 35:255-58.
- Vaughan, J. 1973. Removal of internally deposited plutonium from the skin. Section IX of chapter 10 in *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh, pp. 471-85. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.
- Volf, V. 1963. Treatment of radiostrontium uptake in man. In IAEA 1963, pp. 131-44.
- Volf, V. 1978. *Treatment of incorporated transuranium elements*. A report sponsored by the WHO and the IAEA, Technical report series no. 184. Vienna: International Atomic Energy Agency.
- Volf, V. and E. Gemenetzis. 1977. Removal of plutonium from rats by prolonged administration of chelating agents. In *Recueil des communications—Proceedings*, vol. 4, pp. 1219-22. Proceedings of the 4th international congress of the IRPA held in Paris, April 24-30, 1977. Paris: International Radiation Protection Association.
- Volf, V. and A. Seidel. 1974. Decorporation of ^{239}Pu and ^{241}Am in the rat and hamster by ZnDTPA. *Radiat. Res.* 59:638-44.
- Wager, R. W. and L. A. Temple. 1954. Comparison of CaEDTA and zirconium citrate in promoting excretion of plutonium in the dog. In *Annual report for 1953*, HW-30437. Richland, Wash.: Hanford Atomic Products Operation.

- Wald, N., R. Wechsler, A. Brodsky, and S. Yaniv. 1968. Problems in independent medical management of plutonium-amerium contaminated patients. In *Diagnosis and treatment of deposited radionuclides*, eds. H. A. Kornberg and W. D. Norwood, pp. 575-86. Proceedings of the 7th annual Hanford biology symposium held in Richland, Wash., May 15-17, 1967. Amsterdam: Excerpta Medica Foundation.
- Weber, K. M. 1969. The deleterious effects of EDTA and DTPA on the intestine of the rat. *Z. Gesamte Exp. Med. Einschl. Exp. Chir.* 150:354. [Abstract of Die Schädigung des Darmes durch EDTA und DTPA bei der Ratte, pp. 354-60.].
- Weitl, F. L., K. N. Raymond, W. L. Smith, and T. R. Howard. 1978. Specific sequestering agents for the actinides. 1. N, N', N'', N''' - tetra(2,3-dihydroxybenzoyl)tetraazacylotetra- and -hexadecanes. *J. Am. Chem. Soc.* 100:1170-72.
- Whalen, R. P. and S. Davies. 1972. Americium contamination incident in a New York State Health Department laboratory. *Radiat. Data Rep.* 13:249-53.
- Willard, D. H. 1966. Removal of inhaled radioactive particles. In *Pacific Northwest Laboratory annual report for 1965 in the biological sciences*, BNWL-280, pp. 65-66. Richland, Wash.: Battelle, Pacific Northwest Laboratories.
- Wrenn, M. E. 1977. *Efficiency of orally administered Ca-EDTA from chelation of 210-Pb from the skeleton of the baboon*. Annual Progress Report on NIEHS Center Grant, co-investigators N. Cohn and M. Eisenbud. New York Univ., Institute of Environmental Medicine.
- Wrenn, M. E., ed. 1981. *Actinides in man and animals*. Proceedings of the Snowbird actinide workshop held in Snowbird, Utah, October 15-17, 1979. Salt Lake City: RD Press.
- Wrenn, M. E., N. Cohen, and M. Eisenbud. 1977. *Metabolism of 241Am in accidentally exposed humans*. Annual Progress Report on NIEHS Center Grant. New York Univ., Institute of Environmental Medicine.
- Wrenn, M. E., J. C. Rosen, and N. Cohen. 1972. In-vivo measurement of americium-241 in man. In *Assessment of radioactive contamination in man*, STI/PUB/290, pp. 595-621. Proceedings of a symposium held in Stockholm, November 22-26, 1971. Vienna: International Atomic Energy Agency.
- Zaino, E. C. and R. H. Roberts. 1977. Chelation therapy in chronic iron overload. In *Proceedings of a CIBA medical symposium*. New York: Stratton Intercontinental Medical Book Corporation.

OUTLINE

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Capsule Chronology

- 1913 Hevesy and Paneth use radium D (radiolead) as indicator in analytical chemistry.
- 1920s Blumgart and colleagues at Harvard use radium C (^{214}Bi) injections in humans for study of circulation. Also did a few tracer experiments in man with ^{226}Ra and ^{222}Rn . (These may have preceded the work with bismuth.)
- 1923 Hevesy and Paneth use radiolead as indicator in plant metabolism.
- 1926 Radon-222 "milked" from radium for preparation of radon seeds (Failla, Columbia; and others).
- 1932 Invention of cyclotron, the most used accelerator in medicine and tracer chemistry (see chapter 5).
- 1934 et seq. Tracer chemistry and predecessors of nuclear medicine. Work done around the major accelerator installations (Berkeley, Carnegie, Columbia, MIT,^(a) Rochester, Washington University, and others). Included much instrumentation development.
- 1934 First manmade radioisotopes (Curie and Joliot, France) using alpha particles from ^{210}Po (more in chapter 5).

Berkeley group confirms production of new elements by deuteron and proton bombardments in the new cyclotron (more in chapter 5).
- 1937 Use of radiosodium in man at Berkeley (Hamilton and Stone).
- 1938 Hertz, Roberts, and Evans apply radioiodine to patients. Also do animal studies (MIT-MGH).

Hevesy publishes manual of radioactivity.

Radioisotopes of iron revolutionize ideas of iron metabolism (Hahn, Bale, and Whipple, Rochester).
- 1939 "Medical cyclotron" at Crocker Laboratory, Berkeley, described by Lawrence.
- 1940 Astatine-141 begins to be studied at Berkeley as a possible substitute for radioiodine (Hamilton and Soley).
- 1942 Marinelli formulates basis for calculation of internal dose. It gradually grew in collaboration with Quimby and Hine to become the "classical" system (Memorial Hospital, New York; Columbia University).
- 1944 Radiocolloids proposed as a way to distribute beta-radiation dose to the reticuloendothelial system (Jones, Berkeley).
- 1945 Concept of rep formulated by Parker. Published in open literature later.
- 1946 Iodine-125 isolated.

Distribution of reactor-produced isotopes begun (AEC).
- 1947 First edition of Kamen's classic on isotopic tracers in biology published.

(a) For abbreviations and acronyms, see Appendix D.

- 1948 Hevesy's book on radioactive indicators published.
Marinelli, Quimby, and Hine discuss dosage determination with radioisotopes (Columbia University).
- 1948-1965 The era of therapeutic intent.
- 1949 Chemical principles elucidated for preparation and use of radiocolloids (Gofman, Berkeley).
Controlled selective localization of radiocolloids described in bone marrow, liver, and spleen (Dobson, Berkeley).
Bolus of sodium ^{24}Cl used to measure circulation time (Prinzmetal). Followed by other techniques in the 1950s.
- 1949 et seq. Gallium-72 suggested for bone cancer diagnosis and treatment (Dudley and many workers at Oak Ridge Institute of Nuclear Studies). Later replaced by ^{67}Ga and ^{68}Ga , but these were used in scanning.
- 1950s Cellular-level work begins with tritium and iodine-labeled nucleic acid precursors.
K. Z. Morgan chairs internal dose committees of NCRP and ICRP. Internal dose unit is developed at Oak Ridge.
Parker's proposal for dose units published.
Development of radioactive antibody approach to therapy begins (Bale and Spar, Rochester). Review in 1957.
Astatine work continues at Berkeley (Durbin and Hamilton).
- 1951 Mechanical radioisotope scanner automated by Cassen and coworkers (UCLA). Called a "scintiscanner."
Transmutation effects postulated for ^{32}P in bacteriophage.
- 1952-1955 Idea tried of using neutron capture therapy using radioisotopes as carriers, e.g., boron (Sweet, MGH; Farr, Brookhaven).
- 1953 Considerable further study of gallium for therapy (Brucer, Oak Ridge).
- 1954 Society of Nuclear Medicine (U.S.) organized.
- 1955 Atoms for Peace plan announced. Great increase in availability of radionuclides for all purposes (AEC).
"Gammicon" described (Mueller and Myers, Ohio State). Other instruments for same purpose developed rapidly.
- 1956 More from Hine and Brownell on dosimetry.
Colloidal gold preparations in general use.
- 1958 Scintillation camera described by Anger (Berkeley). A major advance in diagnostics.
- 1959 ICRP/NCRP major publications on limits for exposure of workers to radionuclides.
Publication of description of Anger camera at second Atoms for Peace Conference (held in 1958).
Effect of tritiated thymidine on mouse spermatogonia (Johnson and Cronkite, BNL). Also 1955, 1957, and 1958.

- 1960s** Antibody approach begins at Roswell Park (Pressman, Yagi, et al., Buffalo).
Modification and expansion of ICRP/NCRP dosimetry by Snyder et al.
Much on possible induction of leukemia by radiation therapy for thyroid disorders. Continued through the 1970s.
- 1960** Use of ^{125}I suggested for in vivo scanning of thyroid (Myers, Ohio State). Expanded in 1963 by Harper et al.
Plastic and ceramic microspheres introduced for medical use. Coated with a radionuclide of choice.
- 1961, 1963** Cell renewal processes in human rectal mucosa studied with labeled precursors (Cole and McKalen, Western Reserve University).
- 1962** Iodine-123 suggested for scans in preference to ^{131}I (Myers and Anger, Ohio State and Berkeley).
Tritium-labeled drugs considered for cancer treatment (Marrian et al.).
- 1963** Second edition of Quimby and Feitelberg's book on dosimetry.
Lipkin uses tritiated thymidine to measure generation times and proliferation cycle in cells of human intestinal tract (Cornell and Sloane, Kettering).
Use of $^{99\text{m}}\text{Tc}$ reported for scanning of several organs. Substitute for ^{131}I (Harper et al.). Use grew very rapidly because of large reduction in radiation dose to the patient.
- 1964** MIRD system for internal dosimetry is launched as substitute for "classical" (Marinelli et al.) system.
- 1965-1980s** The Era of Ever-Shorter-Half-Life Materials for use in diagnosis.
- 1965** First try at treatment of leukemia in animals using radiophosphorus (Shkurkin and Lawrence, Berkeley). This is in addition to earlier use for polycythemia vera.
Muller expounds on local use of colloidal gold.
Tritiated water, tritiated thymidine, and ^{60}Co gamma rays compared for ability to induce chromosomal aberrations (Dewey et al., M.D. Anderson Hospital).
High-specific-activity radiocolloids suggested for lung scanning (Wagner, Johns Hopkins).
Oak Ridge symposium on radioactive pharmaceuticals held. Many survey papers (Cloutier et al.).
- 1966** Colloidal properties of lanthanides considered at symposium (Kyker, Oak Ridge).
Iodine-121 and -126 suggested for nuclear medicine uses (Myers, Ohio State).
Bond and Feinendegen conclude that all somatic effects of incorporated tritium are due to radiation dose. No significant transmutation effect in mammalian systems.

- 1966 Radioisotope "cow" developed for "milking" short half-life isotopes from long-life progenitors (Richards, Brookhaven). Commercial production facility developed. Used particularly for obtaining ^{99m}Tc . (A ^{68}Ga positron cow was used in 1964 by Yano and Anger, but much less than the developments of 1966 et seq.)
- 1967 Effect of tritiated thymidine studied on mortality and tumor incidence in mice (Johnson and Cronkite, BNL).
- 1968 First three MIRD pamphlets issued.
Burki and Okada publish on cell killing with tritiated molecules at low temperatures (Berkeley).
- 1969 Krisch and Zelle review work on transmutation effect. Small effect seen in fruit fly.
Special limits proposed for intake of compounds of ^{14}C and tritium (Vennart, U.K.).
Two more MIRD pamphlets issued.
Auger effect of ^{125}I emphasized (Auxier, Krisch, and Zelle).
- 1970s Much work on cellular, subcellular, and carcinogenic effect of tritiated nucleic acid precursors.
Accelerators begin a comeback for production of short-lived isotopes in situ.
- 1970 MIRD pamphlet on decay schemes.
Loevinger's publications on dosimetry.
- 1971 MIRD pamphlets 7 and 8 distributed.
ICRP reports on protection of patients in radionuclide investigations.
Review of uses and availability of cyclotron-produced radionuclides for medicine (Laughlin et al., Memorial Hospital, New York).
Tritiated thymidine reported to produce cancer in mice (Mewissen and Rust, Chicago). Problems with the strain used, however.
- 1973 Feinendegen and Bond find transmutational effect of tritium only when it is incorporated in very specific positions in specific nucleic acid precursors.
Cloutier and Watson write on radiation doses from nuclear medicine procedures.
Potential uses in medicine of ^{241}Am and ^{252}Cf described by Seaborg (Berkeley).
- 1975 Evans traces history of joint Harvard-MIT-MGH collaboration in nuclear medicine.
- 1977 Idea of dose commitment promulgated by ICRP.
- 1978 Simplified version of MIRD system published by Cloutier et al. (Oak Ridge).
Reference Man phantoms prepared by Snyder and expanded by Cloutier.

- 1979 NCRP report on tritiated and other labeled organic compounds incorporated in genetic material.
 Carsten reports series of investigations on tritium in nucleic acid. Definite transmutation effect persists, but only in special situations and in nonmammalian systems (Brookhaven).
 DOE study group on nuclear medicine instrumentation development concludes that governmental support is still needed at the frontiers.
- 1980 MIRD pamphlet 9 distributed (10, 11, and 12 announced).
- 1980s Possible resurgence of therapeutic applications—a possible third era in nuclear medicine with both diagnostic and therapeutic uses active. Includes further use of microspheres, of monoclonal antibodies, epithermal neutrons in combination with ^{10}B , of false precursors, spontaneously fissionable radionuclides, and photoactivation of, e.g., stable iodine.
- 1981 Mathematical and conceptual reconciliation of Marinelli and MIRD internal dose formulations (Robertson, Mayo Clinic, DOE).

Chapter 20

Selected Aspects of Nuclear Medicine and Tracer Chemistry

Overview

As its title implies, this chapter is not a review of either tracer chemistry or of nuclear medicine. It is a review of the ways in which the ideas, people, and installations we have identified in the earlier chapters of this book impinged upon these two fields, and they on them. The role of toxicological considerations is given top billing, and it is shown that either overt toxicity or a desire to minimize patient dose has controlled much of the history of nuclear medicine. These did not play such a key role in tracer chemistry. It is the role of the techniques and ideas developed for radioisotope toxicology and vice versa that are pertinent to the tracer chemistry aspects.

The early enthusiasm for therapeutic uses of radioisotopes is traced, including the "Atoms for Peace Program," and the principal investigators and institutions of the earlier period are summarized. Because of the development of the Medical Internal Radiation Dose system of dosimetry for medical radionuclides, this chapter seemed an appropriate place for a short discussion of dosimetry of radioisotopes, frequently called simply "internal dose" or "internal dosimetry."

Many of the radioisotopes considered are either purposely or through normal processes bound into the precursors of nucleic acids and can have very localized effects within cells. A fairly extensive discussion of cellular-level effects is therefore included. While tritium is given the most attention, iodine, carbon, and others are treated also.

After the broad discussions of dosimetry and cellular-level effects, a series of sections look in more detail at areas of specific work and specific interest. For convenience, these are divided, somewhat arbitrarily, into eras. The first era is the one where therapeutic intent predominantly motivated the research (1948 to 1966). The second era (1966 to date), describes selected aspects of the tremendous growth of uses of radioisotopes for diagnosis, along with the relative decline of new ideas for therapy. The chapter ends with a quick review of some current ideas that could herald a recrudescence of therapy for cancer using radioisotopes and thus perhaps a third era yet to come.

More recent references have been added to this chapter than to many others, many of them in the proofreading stage of the manuscript. Since nuclear medicine is advancing very rapidly, this chapter must pay more attention to recent trends than have some of the other chapters. Nevertheless, it has to be inevitably somewhat out of date. Fortunately, this is history.

I. The Context

A. Purposes

The primary purpose of this chapter is to examine, in a general way, how the research and the investigators concerned with the toxicologic effects of radionuclides in the organism, particularly man, influenced, and in some instances made possible the development of the now enormous fields of nuclear medicine and tracer chemistry.^(a) It is also concerned with the contributions from these fields to the understanding of radionuclide effects and their uses in clinical medicine.

Concern for possible untoward effects of any drug used in diagnosis or therapy or of any agent handled in the laboratory for research purposes always goes hand-in-hand with the development and use of that agent. Thus, we have always had pharmacology and therapeutics accompanied by their obverse discipline, toxicology—sometimes in the thinking and activities of the same individual or group, sometimes in entirely separate groups or even institutions. Sometimes those on the cutting edge of developing new therapies or diagnostic procedures have viewed toxicology and the toxicologist as unwelcome deterrents to progress. However, it is now much more common to see conscientious application, realized or unrealized, by the physician and other professionals of the philosophy of gauging the risk as much as the benefit of any planned procedure.

The dichotomy of balancing desired results against undesired "side-effects" is especially well delineated in the history of the relationships of tracer chemistry, nuclear medicine, and radionuclide toxicology. This is partly because of the high level of concern over radiation effects, e.g., the radium cases (chapter 1), partly because the field developed after some of the gruesome mistakes in chemical pharmacology and therapeutics had come to light.

In the earlier days, the limitations of measuring devices and the lack of choice among available radionuclides made the amounts used even for tracer uses border on toxic levels. Even in applications of tracer chemistry where patients were not ordinarily involved, there was the constant concern that the radioactivity might interfere with the life processes to be studied. Only in the current generation of highly sensitive measuring devices and short half-life isotopes, and readily excreted radiopharmaceuticals has concern for toxic side effects almost disappeared.

This chapter will review historically these considerations and research of most pertinence to the practice of nuclear medicine and the use of radioisotopes as tracers. It will in no sense try to review the history of either nuclear medicine or

(a) This process was started in chapter 5. Let it be clear that we are dealing here primarily with uses of manmade radioisotopes and do not include as "nuclear medicine" the early uses of naturally radioactive materials as therapeutic nostrums.

tracer chemistry themselves. These have been described very adequately by others (e.g., Hamilton 1941 in chapter 5 and later sections of this chapter).

We will begin by tracing the origins and development of the three fields of interest and try to establish a bit of their genealogy.

B. Some Genealogy

In chapter 5, we reviewed the major steps taken in the decade of the 1930s to launch the fields we look at now. The reader is referred there for details of these early steps. To understand better the present situation, we need to trace, in a very broad way, the subsequent lines of development. I have chosen to do this in the form of a crude genealogical analogy.

In terms of the people doing the early work, there is no debate. The three fields (tracer chemistry, nuclear medicine, and radioisotope toxicology) involved the same people to a large extent. Indeed, they were not even separately named. They were one and the same. Hevesy quickly followed his idea of using a radionuclide (natural in origin) as a tracer in chemistry with administrations to plants and then animals. He considered potential effects as well as tracer applications. Robley Evans, among the first and clearly one of the leaders in radioisotope toxicology, put much energy and insight, along with his colleagues at Massachusetts Institute of Technology (MIT) and the Massachusetts General Hospital (MGH), into the development of iodine isotopes for biomedical use. Ernest Lawrence tried on himself some of his newly prepared ^{24}Na to show its rapid appearance in his finger tips. His physician brother John soon tried some of their cyclotron-produced ^{32}P for the treatment of leukemia in mice. Joe Hamilton was quick to apply the newly developed iodine isotopes to thyroid uptake studies and thought deeply of trying therapeutic applications as soon as enough material was available. (Note that this is the same Joe Hamilton who spearheaded the toxicologic efforts of the Manhattan Engineer District [MED] at Berkeley during World War II.)

The question of common ancestry for our three fields needs no further exposition. They are siblings. Should we, like all good genealogists, look for *the* patriarch? Let us try.

Gordon Brownell stated in his 1968 Nuclear Pioneer Lecture: "... the birth of nuclear medicine coincided with the invention of the cyclotron." In terms of having really usable amounts of isotopes available, this is obviously true, the pioneering work of Blumgart (chapter 5) notwithstanding. This would make Ernest Lawrence the father of nuclear medicine. Yet, he would have been the first to deny the honor and defer to others, including his brother John, who stimulated Ernest's interest in biomedical problems and did the first therapy experiment with a manmade radioisotope. Also, both would say it was Hevesy who fathered *the idea* in contradistinction to the machine and the application.

Hevesy was clearly the father of tracer chemistry. Somehow he seems more like a grandfather to nuclear medicine since he was further removed from it. However, he is consistently named as the father of both, and we should possibly accept Hevesy and Blumgart as joint founders of tracer chemistry and nuclear medicine.

Let us turn to the family interrelationships. Obviously, tracer chemistry and radioisotope toxicology are the older siblings. Which is the older is debatable. In terms of describing effects, the toxicology branch takes precedence. In terms of status as discernible disciplines, they seem to be almost twins. Like most

siblings, they did not lead identical or even very similar lives, even though they lived in the same household for many years. They used the same instrumentation and shared much methodology. Each attracted disciples. Because of the enormous usefulness of the tracer technique in all aspects of biomedical research, tracer chemistry became so popular that it had many more friends and playmates than radioisotope toxicology. However, there were few occasions where one sibling felt any need to horn in on the other's affairs. Instead, they helped each other.

Tracer chemistry had many sources of satisfaction as it developed to be the handmaiden to nearly all branches of natural science. The presence of scintillation detectors and the paraphernalia of tracer chemistry in the halls and laboratories of an institution gives one few clues as to what department one is in.

With the youngest sibling, nuclear medicine,^(a) the old homestead was only a comfortable incubator. Again, techniques, instrumentation, ideas, and people were shared initially. However, the field attracted a convergence of chemistry, electronics, nuclear physics, physiology, biochemistry, pharmacology, and medicine that quite outgrew the old habitat. Techniques, particularly the more recent techniques for use in diagnostic tests, have not only achieved remarkable sophistication (and bulk) but are in use in thousands of hospitals throughout the world. The old institutional research connection could not fully accommodate the youngest sibling.

In a sense, both tracer chemistry and nuclear medicine have been happy fields. Tracer chemistry has helped to unravel many of nature's secrets. Despite some disappointments (see later sections), nuclear medicine has placed undreamed-of resources in the hands of the physician and medicine in general. One of the field's pioneers and the historian of the Society for Nuclear Medicine, Dr. William G. Myers of Ohio State University, likes to refer to the scintillating images of distributions of radioisotopes used in diagnosis as "twinkling" atoms and imaging as "inside-out" radiology (Myers 1981a,b). Happy terms from "scintillating," happy people.

There have been occasions when the radiation toxicology (health physics) branch of the family felt the nuclear medicine branch was in need of both help—which came in the form of a flood of reactor-produced radionuclides—and some cautions about the chances some of their younger members seemed inclined to take with radiopharmaceuticals. However, it was no feud, and it resulted primarily in additional self-policing and a few not-too-welcome admonitions from the regulators.^(b)

The above should not imply that the radiation toxicology branch of the family never had any fun. Surely the thrust of this book shows that many people found it interesting, important, and worth supporting. But the enterprise has required, by and large, the hospitality of major institutions and the financial support of outside agencies, especially government, since its subjects could not be billed for services rendered. To follow our family analogy, the radioisotope toxicology branch has been more of a "stay-at-home." It has remained in surroundings more like the old homestead. Nevertheless, the family ties are still viable.

(a) The term "nuclear medicine" is ascribed to Robert Newell, the somewhat irascible but beloved radiological physicist who worked for many years at Stanford University.

(b) Remember that regulation, as it applies to the nuclear industry or to laboratory uses, does not apply to nuclear medicine, except for licensing and such things as waste disposal.

There are those who view the wartime emphasis on toxicology as an unfortunate diversion from the main tasks of developing medical uses. Now there are also those who feel little need to think of toxic side effects of the entities they are using. This is justified with current techniques, in part. However, it came about because of the constant search to do the job with ever smaller radiation doses. To do this required vigilance, humility, and close attention to possible toxic side effects.

Before going on, we should look back briefly at the phases in isotope sources. As already stated, there would have been no nuclear medicine and much less tracer chemistry but for the cyclotron, which inhabited the old homestead. While many of the radioisotopes produced were of such short half-life that all-night experiments were the rule,^(a) many of the radionuclides were too energetic and of too long half-life for optimal utilization. This led, in part, to the development of specific compounds that would carry the radionuclide to the desired area, preferentially, and then leave rapidly. Thus the field of radiopharmaceuticals was born.

At the end of World War II, a bonanza of radionuclides was made available from Oak Ridge and later from Brookhaven under the Atoms for Peace Program described in earlier chapters and later in this chapter. The idea then was therapeutic uses more than tracer applications. If the cyclotron helped to father nuclear medicine and tracer chemistry, the reactor should be dubbed their rich uncle.

This bonanza continues, but is now being modified by a return to cyclotron-produced isotopes with low-energy gamma rays and frequently no short-range radiotoxic beta-particle emissions. The object is further reduction of radiation doses (again under the influence of that sterner member of the family—radiation toxicology).

Modern technology has put small accelerators within the reach of many hospitals, both in the major centers and, it is anticipated soon, in community-type hospitals. With manufacture of radionuclides *onsite* possible, the problems of ordering, shipment, etc., can be reduced, and very short half-life materials can be used. This further reduces the collective radiation doses.

Despite these developments, it seems unlikely that the progeny of nuclear medicine will want or be able to forsake completely the old homestead with its assemblage of disciplines. Meanwhile, the lusty youngest sibling is contributing much in the way of instrumentation and methodology and in ideas to the other members.

C. Diagnosis Versus Therapy

The early applications of radionuclides in medicine were strongly weighted toward therapeutic uses. The analogy to Paul Ehrlich's "magic bullet" idea that developed around Salvarsan and the chemotherapy of syphilis influenced much of the early thinking and planning. This took two forms: (1) the utilization of radionuclides that were already known from the toxicologic work to localize strongly in certain organs, and (2) the preparation of compounds whose chemistry would dictate their specific localization in a tissue, particularly a tumor, and which could be labeled with sufficient amounts of a suitable radionuclide to deliver a therapeutically effective radiation dose to the tissue or organ.

(a) "From cyclotron to vein" was an apt aphorism (chapter 5).

The best early example of the first type was, of course, radioiodine. It was found, somewhat after the early tracer work, that large doses of iodine could be used in place of surgery for reduction or ablation of the thyroid gland in hyperthyroidism.

Another application was based on the idea that iodine would seek out and deposit in thyroid tumor tissue even when that tissue was in the form of metastases of a thyroid cancer sometimes far removed from the gland itself. This application was only moderately successful. There was considerable variability in the avidity with which metastases of thyroid cancers took up radioiodine. Sometimes large radiation doses could be given to the tumor tissue no matter where it had spread to. Sometimes the amount of uptake and resulting treatment success were disappointingly low. Much work was needed to establish optimal protocols.

Phosphorus-32 had been found through animal studies (again by those primarily interested in toxicology) to deposit largely in bone and bone marrow. The beta particles emitted were sufficiently energetic that the deposits in bone mineral irradiated marrow for a considerable period. It was on this basis that Lawrence and his colleagues (Shkurkin and Lawrence 1965) made that first try at the treatment of leukemia in animals. Therapy with radioactive phosphorus was reasonably successful in some blood disorders in humans—perhaps most outstandingly for polycythemia vera, a malady characterized by overproduction of red blood cells. Now such treatment has settled down to being more palliative than permanently curative (Shkurkin and Lawrence 1965) but is important nevertheless.

There are many other cases where a radionuclide has been chosen for therapy because of its tendency to localize in a given organ or tissue. We will examine some of these more specifically in subsequent sections. However, only a few have become permanent members of the therapeutic armamentarium. To realize maximum benefits, the doses frequently had to be quite large. Unwanted radiation of normal tissues was a constant problem—with all that means in side effects and general toxicity. Frequently, the target tissues became radioresistant^(a) or lost their avidity for the radionuclide in question.

In part, because of these problems, the carrier techniques were developed. The earliest of these and the one used most in early therapy involved radiocolloids. Using the knowledge gained in the general study of radionuclide metabolism and knowing the important role of the colloidal state in governing distribution and excretion, described in several earlier chapters, it was decided to exploit the normal functions of the reticuloendothelial system (RES) to bring about localization of radiation dose. The philosophy of internal radiocolloid therapy and specific examples are summarized well by Muller (1965). Colloidal radioactive gold is among the most successful of these, but radioactive chromic phosphate and several other preparations have had moderate popularity.

The principle here is, of course, to use the physicochemical properties of the colloid to determine tissue localization (e.g., uptake by components of the RES), then let the radioactivity “come along for the ride” rather than depending upon the chemical bonding of the radionuclide itself to the target tissue or cells. These have been especially successful for more or less superficial lesions to

(a) Development of radioresistance is, of course, a common problem in therapy using external radiation sources.

which the colloid could be applied. They have their problems for systemic use. It appears that only colloidal gold preparations possess almost no toxicity to complicate their use.

A different approach harks back to the radioactive microspheres we discussed in the chapters on pulmonary radiotoxicology. Suitable labeling of some of these microspheres is relatively easy because of their considerable stability. They have found many uses, which we will discuss presently, but most of them are still quite experimental.

Finally comes the more conventional radiopharmaceutical—a compound, nearly always organic, with affinity for a given tissue or organ and which can be labeled. These have not found much use in therapy because the thrust has been to develop compounds that will leave the body rapidly for diagnostic uses. Also, many of these compounds are readily destroyed by the intense radiation field needed for therapeutic applications.

Meanwhile, on the diagnostic side, things have been booming. Much of the work had its roots in radioisotope toxicology, but it soon began an independent existence. Three developments underlay these phenomena: (1) the growth of the radiopharmaceutical industry; (2) the production of short half-life radionuclides, many of which decayed by Auger electron production or other processes and had a minimum of beta radiation but sufficiently energetic x or gamma rays to make external counting easy; and (3) tremendous strides in measurement abilities. Two excellent summaries of the characteristics and the problems of radioactive pharmaceuticals are seen in chapters by Wagner and Emmons (1966) and by Charlton (1966), respectively, which led off an Oak Ridge symposium on radioactive pharmaceuticals.

As part of the chapter by Wagner and Emmons, a concept defined as the "Figure of Merit" is described. In its simplest form, this is the ratio of the dose to the target to that in the nontarget tissues. The higher this ratio, the better the pharmaceutical—as our toxicologic experience would have dictated. Also involved in design or selection of an ideal radiopharmaceutical are: maximum permissible radiation dose, time course of uptake and elimination from target and nontarget tissues, optimum time needed for measurements, and others.

Among the problems (Charlton 1966) are radionuclide purity, chemical form and stability, sterility (e.g., freedom from pyrogens), etc., as well as ease or difficulty of preparation and handling.

Yet another approach developed during the 1950s utilizes antibodies and the immune system and has been applied to both diagnosis and therapy. Nothing could be more specific than a specific antibody. If the target organ were cancerous and an organ- or tissue-specific antibody could be loaded with a significant dose of radioactivity and seek out the neoplastic tissue specifically, a potent therapeutic weapon might result. A considerable effort went into approaches comparable to, but more complex than this, especially in the hands of William F. Bale and his colleagues at the University of Rochester (see section IV 7 of this chapter; Bale and Spar 1957).

On the diagnostic side, analytic methods were developed called radio-immunoassays that could detect and measure minuscule concentrations of physiologic substances at levels unmeasurable by other techniques. This contrasts to most of the other diagnostic techniques of nuclear medicine that we have been enumerating by being an *in vitro* procedure. It was originated by Solomon Bersont and Nobel Prize winner Rosalyn Yalow (see *Seminars in*

Nuclear Medicine, Vol. 5, No. 2, 1975, for review and several references; also Myers and Wagner, 1975).

These developments have involved the private sector of our economy more than any of the areas we have examined so far in this book. The combination of suitable chemistry in the vehicle, suitable radionuclide properties, and ever more sensitive and automated measuring systems has resulted in the diagnostic uses becoming the major part of modern nuclear medicine and a booming industry for the instrument makers.

It must be said that on the whole the applications of radioisotopes for the treatment of disease have not fulfilled their initial promise.^(a) The field has narrowed to a few successful procedures. Unfortunately, it was the problems of toxicology and lack of specificity that underlay much of this retrenchment. The dose simply could not be localized sufficiently well or untoward sequelae averted dependably.

In contrast, the doses and toxic counterparts on the diagnostic side have been reduced drastically.

D. Who and Where

The early work in nuclear medicine and tracer chemistry in the United States emanated from the major centers we have been visiting throughout this book, particularly those of the early years, e.g., Harvard, MIT, MGH, and the University of California at Berkeley to start with. It went wherever cyclotrons were built. This soon added the University of Rochester, Washington University of St. Louis, and, later, Columbia University, and the Carnegie Institution in Washington.

The people, too, were the old familiar group. But this was not for long. Tracer chemistry was soon involved wherever modern physiology and biochemistry were being done. Medical applications did not spread so rapidly. They kept on steadily in the major centers throughout the years of World War II but did not spread throughout all of medicine until much later. Indeed, there was some question into the middle 1950s as to whether what we now call nuclear medicine should remain as a segment of radiology or a separate discipline in medicine. The prefix "radio" pushed it toward radiology as did the fact that most of the advances were being made by radiologists. However, internists, pediatricians, neurologists, even surgeons were coming to depend on the diagnostic services the new field could perform. As Myers and Wagner stated (1975), many felt that the surest way to encourage growth and be a resource for all of medicine was to recognize the activities as an entity. The Society of Nuclear Medicine was formed in 1954. The rest is history.

The number of diagnostic tests using the techniques of nuclear medicine is now several million per annum in the United States alone and would be still more if we include radioimmunoassay procedures. Yet, the lusty sibling really never fully forsook the old haunts. The American Board of Nuclear Medicine is a "conjoint entity" sponsored by three boards: Radiology, Internal Medicine, and Pathology (Myers and Wagner 1975). Three types of certification are possible—one in the whole field, one in nuclear imaging (administered by the American Board of Radiology), and one in radioisotope pathology

(a) It was originally considered enormous.

(administered by the American Board of Pathology). Our present and past radioisotope toxicology is most closely related to, although not identical with, the last named, of course.

In most institutions, one will find the nuclear medicine enterprise physically located hard by diagnostic radiology. Radiation therapy and therapy with radioisotopes are not always close by. The separation of diagnostic and therapeutic functions is becoming ever more general.

The balance of this chapter will engage us with some detailed examples of the generalizations made in this section.

II. Dosimetry

We have had relatively little to say so far in this book about the calculation of radiation dose from internally deposited radionuclides, except for some applications to maximum permissible intakes and standard setting in chapter 16. It is time now to review the subject briefly.

Obviously, nearly every experiment we have discussed has required or would have benefited from some sort of estimate of dose. In only a few instances, e.g., the work of Miriam Finkel, at Argonne National Laboratory (ANL), has the dose been rigidly couched in terms of the administered amount of material in the standard style of chemical toxicology or, as a permissible body burden in microcuries as Evans developed for radium (chapters 1 and 16). The hundreds of experiments we have reviewed gave us raw data in activity units per unit mass. The majority ended up, however, with translation of these to an absorbed dose in rad or rem,^(a) although sometimes in fractions of the maximum permissible dose (chapter 12). This has occurred in our field of interest because doses of external radiation were already expressed in physical units related to energy flux or absorption. The radioisotope people could not bear to have their results remain for long in units that could not be compared to external radiation. Indeed, frequently the same people did both kinds of work, and it was natural to want the same terms. The result was a system of calculations commonly called "internal dosimetry," "internal emitter dosimetry," or simply "internal dose."

The purposes are laudable, and the results have, on the whole, been very useful. A rather extensive research effort has been built up around them and should be reviewed.^(b,c)

In addition to putting research results with deposited radioisotopes in a form that allowed comparison with the huge literature using external radiation sources, another important reason was the needs of medicine. Even the earliest applications of radioisotopes in diagnosis and therapy inevitably required some system for estimating the associated radiation dose. The early development of the core system for internal dosimetry sprang in large part from the radiological physicists associated with biomedical installations, particularly medical centers.

(a) See Appendix D.

(b) We have waited for this chapter on nuclear medicine to compare the systems developed, even though they have broad application to much of this book, because of the development of the "MIRD" (Medical Internal Radiation Dose) system to be described.

(c) We should note how much further this system goes than does conventional toxicology, where frequently all that is given is the amount of material administered; not even, until very recently, the amount accumulating in a given organ or tissue.

It is not possible in this book to describe details of the schema of internal dosimetry; they are well summarized and easily available elsewhere. We will, instead, look at the basic nature of the schema and some of the problems associated with their use.^(a)

A. The Classical System

All of the formulations of the 1940s and 1950s, and into the early 1960s, utilized a system based on early formulations of Marinelli at Memorial Hospital in New York (Marinelli 1942) and subsequent work by Marinelli with Edith Quimby at Columbia University and C. J. Hine at Memorial Hospital (Marinelli, Quimby, and Hine 1948). A chapter on radioisotope dosimetry (classical type) was prominent in the first texts on nuclear medicine—a good example being the one by Moses Greenfield in the book edited by Blahd (Greenfield 1965). A pithy summary of the development of radiation dosimetry, with examples involving both external sources and radionuclides in tissues, is given by Quimby as the first chapter in an Atomic Energy Commission (AEC) symposium held at Oak Ridge in 1969 (Quimby 1970).

The system was applied early to the beta particles from ^{32}P . It involved development of a unit for tissue absorption to be the equivalent of 1 roentgen of x rays in air (Marinelli, Quimby, and Hine 1948). This was called the equivalent roentgen (e.r.).^(b) It was calibrated in terms of the necessary number of beta particles of a given average energy needed to produce the same amount of ionization in 1 g of tissue as is produced by x-ray photons delivering 1 roentgen in air. Obviously, to obtain the total number of beta particles released per unit volume of tissue, it was necessary to know the kinetics of both physical decay and biological elimination, tissue distribution, etc. We saw instances of the importance of these and other parameters in chapter 16 and noted the fact that the numbers had been provided largely by the radioisotope toxicology people.^(c)

(a) *Note added in proof:* In the interim between completion of this chapter and publication of the book, the National Council on Radiation Protection and Measurements issued a report (NCRP 1985a) that includes a careful review of some of the history reviewed in the following pages. It is, in some ways, more sophisticated, in that it ties the internal dosimetry procedures more overtly to the practices developed for measuring external radiation, particularly radium gammas. The chairman of this committee was James S. Robertson, Department of Energy (DOE), whose role is mentioned briefly in the text that follows herein. If this report had been available when this chapter was written, the dosimetry section could have been somewhat shorter. Nevertheless, there is only a modicum of undesirable overlap between the two documents.

(b) This is very similar to the “rep” or “roentgen equivalent physical,” which Parker developed at Hanford during the MED days. This had to await declassification to be known widely in the medical area (see Parker 1950), and the “e.r.” designation was used meanwhile by Marinelli et al. The rep was actually used much more in subsequent years. See Evans (1948) for conversion of reps to absorbed doses in tissues and more on its use.

(c) Very useful handbooks were produced within the government-supported laboratories that made the handling of radioisotopes and the calculation of doses considerably easier. A very early document to the open literature was a table of isotope decay prepared by Bruner, King, and Smyser (1951). Later, the Bureau of Radiological Health of the U.S. Public Health Service (PHS) produced its *Radiological Health Handbook* largely as a training aid that became a basic reference and major resource in the health field (see BRH-NTIS 1970). These and numerous others, plus the reports of the ICRP, NCRP, and MIRD have provided invaluable source material in usable form. A basic table of isotopes was produced even earlier by Seaborg and Perlman (1948).

The principles and how the equations got reduced to fairly simple shorthand renditions are well depicted in the chapter on dosage calculations for radioactive isotopes in the monograph by Quimby and Feitelberg 1963). This system was the basis of the formulations in Publication 2 of the International Commission on Radiological Protection (ICRP 1959). Partly because of this step and partly because of the development of a system for gamma emitters by the same group, which was used for many years, what is termed here "The Classical System" was historically called "The Marinelli System," sometimes the "ICRP System," and sometimes the "Marinelli-ICRP System."

Illustrations.^(a) The system was quite simple in cases where the radiation arose from sources such as alpha emitters, relatively low-energy beta emitters, or from other sources with short path lengths in tissue. It was assumed that distribution of the radioisotopes was uniform within the organ, that the organ was homogeneous, and that all energy was absorbed within the organ or tissue.

1. Dose rate from nonpenetrating radiation.^(b)

$$\text{Rads/day} = \frac{(\text{d/min}/\mu\text{Ci}) \times (\text{min/day}) \times (\bar{E} \text{ in MeV/day})}{\text{weight of organ} \times \text{MeV/100 ergs}} \times C_0$$

where C_0 = initial concentration of activity in the organ or tissue

\bar{E} = average energy in MeV/disintegration

1 erg = 6.25×10^{11} eV

100 ergs = 6.25×10^{13} eV

1 rad = 100 ergs/g = 6.25×10^7 MeV.

If we are interested in daily dose, and *there is no appreciable loss of activity during one day*, the above can be shortened to $51 C \bar{E}$ where $C = \mu\text{Ci/g}$ and \bar{E} = average energy.

The answer is in rad if the energy term refers to physical energy alone, but in rem if the energy term has been corrected for the relative biological effectiveness (RBE) of the radiation emitted (in which case it is called "effective energy").^(c)

(a) These illustrations were developed in part by Dr. John Hursh and this author in a course given at the University of Rochester and do not rigorously follow the symbols and formulations of Marinelli (1942) or Marinelli, Quimby, and Hine (1948), but they use the same principles.

(b) Does not penetrate beyond the source organ (organ of deposition).

(c) The expression for effective energy has undergone several changes with time. In the earlier formulations, it was the sum of the physical energy (average), times a factor F to account for the ratio at time t of disintegrations from any daughter products that remain in the target organ to the disintegrations of the parent, the RBE and a factor n , which applied to bone seekers and reflected their relative toxicity as we discussed in much detail in chapters 7, 8, and 16. In later formulations, the term RBE was replaced by the Quality Factor (QF or Q) to reflect the fact that it was an arbitrary number based on linear energy transfer and might or might not represent the actual RBE in a given biological system. In still later formulations, to be discussed in a later section, the entire term became "Specific Effective Energy" (SEE). When these modifying factors are used, the unit of the final answer is the "rem" whose origin has an interesting history (Parker 1981). It can be translated as "roentgen-equivalent man" or "roentgen-equivalent mammal" if need be.

2. Total dose, assuming energy absorption is totally within the organ of interest.

$$D_{\text{(rads)}} = \frac{C_0 \times (\text{d/min}/\mu\text{Ci}) \times \bar{E} \times 1.44 T_e \times \text{min/day}}{\text{weight of organ} \times 6.25 \times 10^7 \text{ MeV/g/rad}}$$

where $C_0 = \mu\text{Ci}$

\bar{E} = Average energy (effective)^(a)

T_e = effective half-life in days (see attached derivation).

This is sometimes shortened to:

$$D = 73.8 C \bar{E} \tilde{T}_e (1 - e^{-\lambda_e t})^{(b)}$$

if C_0 is in microcuries, and half-lives are in days.

The expression \tilde{T}_e refers to the mean lifetime ($1.44 \bar{T}_e$), whose derivation is given in a separate section below. The decay constant λ_e is the effective decay that includes both radioactive decay and biological loss.

3. Effective half-life—Radionuclides are lost from the body by two processes: physical decay and biological loss,^(c) mainly excretion.

It is convenient to assume that the latter is first-order with respect to time, similar to radioactive decay. Thus, we can express biological loss rate as:

$$-\frac{dN}{dt} = \lambda_b N$$

and total loss as:

$$-\frac{dN}{dt} = (\lambda_p + \lambda_b) N$$

where N = no atoms

λ_b = biological loss constant

λ_p = physical decay constant

We can combine $(\lambda_p + \lambda_b)$ into λ_e , the effective loss constant.

$$\text{Biological half-life} = T_B = \frac{0.693}{\lambda_b}$$

$$\text{Effective half-life} = T_E = \frac{T_p T_B}{T_p + T_B}$$

where T_p is the physical half-life.

(a) See footnote (c) on previous page.

(b) The constant 73.8 is the product $(3.7 \times 10^4 \text{ dis}/\mu\text{Ci}/\text{sec})(1.6 \times 10^{-6} \text{ erg}/\text{MeV})(10^{-2} \text{ rad}/\text{erg})(86,400 \text{ sec}/\text{day}) 1/\ln 2$.

(c) In some older literature, the term "biological loss" represented total loss and what has been called biological loss above was called "excretion loss," with symbols suitably confusing. This did not last long, but may be encountered in early papers.

4. Mean lifetime—We cannot use the half-life concept to find total number of atoms disintegrating, because half-life is a statistical concept. Any given atom might disintegrate anytime from now to infinity. To have a useful figure, we must use an expression called “mean” or “average” lifetime.

The number of atoms breaking up in interval t to $t + dt$ is

$$\lambda N_t dt \text{ or } \lambda N_0 e^{-\lambda t} dt.$$

The total lives of all these atoms added together is the total number times the life of each or

$$\lambda t N_0 e^{-\lambda t} dt$$

or the integral from 0 to ∞ of the totality of atom lives divided by N_0 (the original number of atoms).

$$\begin{aligned} \text{Av. life} &= \frac{1}{N_0} \int_0^{\infty} \lambda N_0 t e^{-\lambda t} dt \\ &= \left[-te^{-\lambda t} - \frac{1}{\lambda} e^{-\lambda t} \right]_0^{\infty} = 0 + \frac{1}{\lambda} \end{aligned}$$

$$\frac{\Sigma \text{ all lifetimes (atom years)}}{\text{Total number of atoms}} = \frac{N_0}{\lambda N_0} = \frac{1}{\lambda}$$

$$\bar{T} = \frac{1}{\lambda} = 1.44 T$$

$$\text{Since } \lambda = \frac{0.693}{T}, \frac{1}{\lambda} = \frac{T}{0.693} = 1.44 T$$

5. Still considering situations where all of the energy is absorbed in the organ containing the radionuclide, it is also possible to formulate a calculation for the dose over a given interval of time, but this carries us beyond the purposes of this short historical review. It can be seen in cited reviews.

6. Penetrating radiations—With photon rather than particulate radiation, the assumption that all of the energy is absorbed in the organ of interest will usually be incorrect. Also, the calculation of absorbed dose in organs from a gamma-ray source external to the body could not be done on the same basis as the exposure dose used for x rays. Much of classical dosimetry for radioisotopes grew up around these problems.

The approach for radionuclides within the body can be illustrated by an excerpt from the chapter on dosage calculations for radioactive isotopes in the text by Quimby and Feitelberg (1963):

Gamma Ray Emitting Nuclides in the Body. In the case of gamma rays emitted within an organ or anywhere within the body, absorption is rarely complete within the tissue of interest. The approach to the dosage problem must therefore be different from that for beta rays.

When the nuclide is distributed throughout a volume of tissue such as V [see figure 20.1] . . . with a concentration of C μCi per gram, the dose rate per hour at any point P due to the quantity of radionuclide CdV present in a small volume at a distance r from P will be

$$d(dy) = \frac{10^{-3} \Gamma C e^{-\mu r}}{r^2} \text{ roentgens per hour,}$$

[The symbol Γ is the "specific gamma ray constant" in units of $\text{R/hr-per unit of activity at 1 cm.}$]

where μ is the *effective* absorption coefficient of the radiation per centimeter of tissue. The value of this absorption coefficient depends on the fraction of the scattered radiation which is absorbed within the tissue. Its evaluation is very complicated, but fortunately, for absorption in unit density material it is essentially constant, and less than 0.03 cm^{-1} for gamma ray energies in the range from 0.1 to 2.0 Mev. (The dose rate for $1 \mu\text{Ci}$ at 1 cm is $10^{-3} \Gamma$.)

The total dose rate at point P then is

$$dy/(\text{hr}) = 10^{-3} \Gamma C \int_V \frac{e^{-\mu r}}{r^2} dV \text{ roentgens per hour.}$$

This expression is not readily integrated except when the volume is a sphere, but it can be evaluated for some other shapes. It may be called the *geometrical factor* and represented by g . In any volume the value of g will depend on the position of the point of reference, being a maximum at the center and a minimum at the surface. Usually what is desired is an average gamma dose rate, and for this purpose it is desirable to define an average geometrical factor, \bar{g} . For a sphere of unit density material, of radius R ,

$$\bar{g} = 3\pi R, \text{ for radii up to 10 cm.}$$

The total gamma ray dose, Dy , is . . . $dy/(\text{hr})$ multiplied by the average life in hours:

$$Dy = 10^{-3} \Gamma C \bar{g} \times 1.443 \times 24 T = 0.0346 \Gamma C T \bar{g} \text{ roentgen,}$$

[The constant 0.0346 is the product of $(10^{-3}/\mu\text{Ci})(24 \text{ hr/day})$ and $(1/\ln 2)$.]

where T is the half life in days.

(Quimby and Feitelberg 1963, pp. 116-118)

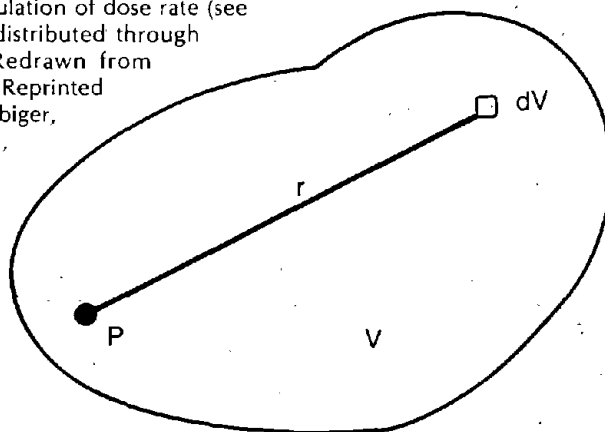
Clearly, the fact that gamma ray attenuation is exponential means that the fraction of energy absorbed within a tissue or organ will never quite reach 1, although it may approach 1 closely.

Comment on the Classical System. The above represents more than the original Marinelli concept and formulation. There has been much extension to include work done by the committees of the ICRP and NCRP (see chapter 16) and others in the toxicology and radiation protection fields.

Many of these extensions came first from work in the MED.^(a) Obviously, those concerned with setting of exposure standards had to work in the war years under the security restrictions of the MED. They developed systems for immediate application to radiation protection (i.e., health physics). Postwar publication of these showed the extent and elaborateness of their work. It went

(a) See earlier chapters.

FIGURE 20.1. Basis for calculation of dose rate (see text) from gamma-emitter distributed through large volume of tissue. (Redrawn from Quimby and Feitelberg 1963. Reprinted with permission of Lea and Febiger, Philadelphia, Pennsylvania, copyright 1963.)



far beyond the original "classical" system in its application to radioisotopes (Morgan 1947; Cohn 1948). The calculations were extended to exposition of maximum permissible body burdens and maximum permissible concentrations of radionuclides in air and water for occupational exposure, as we saw in chapter 16. They can be seen in the reports of the ICRP (1959) and the NCRP (1959). Other expositions can be found in Hine and Brownell (1956), which contains several review papers; Reports 10a and d of the International Commission on Radiation Units and Measures (ICRU 1962a,b); Spiers (1968), especially chapter 3; Mayneord (1950); Morgan and Turner (1973), especially chapter 10 by W. S. Snyder (Snyder 1973); and the various textbooks of health physics.

As formulated, the system most widely used in radiation protection was locked into the concept of continuous intake and limitation of exposure to a critical organ or tissue. Later it was redone to accommodate single rather than continuous intake. However, the end result was still aimed at the maximum allowable burden or permissible exposure.

Physicians wishing to calculate the dose to their patients could do so using rule-of-thumb formulations. However, it was very difficult to calculate the dose to one organ from radionuclides deposited in another without making many unduly simplifying assumptions. Frequently, more than one type of irradiation was emitted by the deposited radionuclides. Body organs are irregular in shape and far from homogeneous, despite the assumptions made. The assumption of uniform distribution bothered many, since distribution is seldom uniform. Also, the assumption of a single exponential function of time to describe retention (i.e., the single effective half-life) was frequently only a convenient fiction. In some organ complexes, build-up of secondary radiations had to be accounted for as a function of distance from the source. Also, nuclides emitting both beta and gamma radiations required separate calculations.

None of these problems was insoluble with the classical system. Indeed, starts were made on all of them. We can see examples in the chapter by Snyder (1973) and by Saenger and Kereiakes (1971). Nevertheless, preoccupation^(a) of the classicists with radiation protection situations and the growing complexity of

(a) Probably more perceived than real.

their operations led those working in nuclear medicine to feel they had to devise a scheme more responsive to their perceived needs.^(a)

B. The MIRD System

In November 1965, Edward M. Smith, a physical scientist on the staff of the Hospital for Special Surgery affiliated with the Cornell University Medical College in New York, delivered a paper at the Oak Ridge symposium on radioactive pharmaceuticals (Smith 1966) that discussed the various problem areas of absorbed-dose calculations when applied to pharmaceuticals rather than inorganic salts. This paper stressed the lack of good biological information on the behavior in vivo of radioactive pharmaceuticals. It served to encourage the further development of an independent approach to internal dosimetry and attracted the support of the Society of Nuclear Medicine. As such things always do, it led to the formation of a committee, the "Medical Internal Radiation Dose" (MIRD) Committee of the Society of Nuclear Medicine. A group had been organized in 1964, and, from 1965 on, it went all out for a comprehensive system tailored to medical (i.e., clinical) problems and uses. A series of papers published for the most part in the *Journal of Nuclear Medicine* were bound together as pamphlets (called MIRD pamphlets), the first being issued in February 1968.

Smith moved to the University of Miami soon after the Oak Ridge meeting, and he became the first cochairman and then executive director of MIRD. Smith explains the basis for MIRD as an introduction to pamphlets 1, 2, and 3. Excerpts are given below.

In October 1964 the president of the Society of Nuclear Medicine, John Hidalgo, initiated an ad hoc committee of the Society to serve the needs of nuclear medicine in the determination of the radiation absorbed dose to patients who are administered radiopharmaceuticals. An active group within the Society agreed that data and information available to the profession at that time were not adequate to determine to the desired accuracy the absorbed dose resulting from the use of radioactive materials in diagnostic studies.

The tissue distribution data relating to biologically-distributed radionuclides had been gathered primarily for the purpose of establishing health safety standards for workers exposed to elemental forms of the radionuclides rather than for specific chemical forms (radiopharmaceuticals). There existed established techniques for determining the absorbed dose delivered by external or by encapsulated interstitial radiation sources for therapeutic purposes, but the data needed to calculate internal radiation absorbed dose due to biologically-distributed radiopharmaceuticals with the degree of confidence that physicians preferred were scattered and not easily available. Also there was doubt that the data were the best that could be generated in view of new developments in nuclear spectrometry, computerized absorbed-dose computation techniques and improved measuring techniques for determining the tissue distribution and life-times of radiopharmaceuticals in patients. In addition, the increase in the use of radionuclides that emit low-energy photons presented some serious problems to the accepted methods of calculating the absorbed dose.

Mr. Hidalgo, with the encouragement of C. Craig Harris, organized the committee with Drs. Monte Blau and Edward M. Smith as co-chairmen. Both were active in

(a) A report by ICRP, *Protection of the Patient in Radionuclide Investigations* (ICRP 1971), addressed the physicians' problems, perhaps somewhat belatedly, and, unfortunately, it did so in a nonquantitative manner.

the search for better and more reliable methods of estimating the absorbed dose to patients resulting from the diagnostic use of radionuclides. Dr. Blau assumed direction of the branch of the committee concerned with biological data, and Dr. Smith headed a team primarily concerned with the physical aspects of the problem.

The objective of the committee, stated at its first meeting, was and still is:

To provide the best possible estimate of the absorbed dose to patients resulting from the diagnostic or therapeutic use of internally administered radiopharmaceuticals with the restriction that the committee make no judgment as to the medical significance of the estimated absorbed dose.

In order to achieve the above objective, the committee has proposed to develop, collect and critically evaluate information in the following areas:

1. Formulae, units and symbols that are consistent for absorbed-dose calculations by either manual or computer techniques.
2. Physical and nuclear decay-scheme data needed as input for the formulae developed.
3. Metabolic data on the distribution and life-times of radiopharmaceuticals at the total-body, specific-organ, sub-organ and micro-organ level where necessary as well as the influence of the patient's age and clinical state on these variables.
4. Chemical, radiochemical and radionuclidic purity and stability and physical characteristics of radiopharmaceuticals when they are apt to affect the absorbed dose to the patient.
5. Accuracy of the calibration methods used for determining the activity of a radiopharmaceutical.
6. Anatomical and physiological data for patients of various ages and body types.

In the fall of 1965 the Society was awarded a grant by the National Center for Radiological Health of the U.S. Public Health Service (at that time the Division of Radiological Health) to support the work of the committee.

Since the beginning of 1967 the committee has been actively working with the Food and Drug Administration in the evaluation of absorbed dose and other related areas. Efforts are being made to establish a master file of biological data and absorbed-dose calculations that will be deposited with the Food and Drug Administration and made available to the radiopharmaceutical manufacturers as an aid in preparing their package inserts. Representatives of the radiopharmaceutical industry were invited to attend the June 1967 committee meeting as observers. (Smith 1968)

A list of the membership of MIRD between its formation and the issuing of the first pamphlets is given below.

Members of the Medical Internal Radiation Dose Committee (1964 to 1968)

Cochairmen

Edward M. Smith, University of Miami
Monte Blau, Roswell Park Memorial Institute

Secretary

Jonathan P. Miller, Abbott Laboratories

Members

Martin J. Berger, National Bureau of Standards
Mones Berman, National Institutes of Health
Gordon L. Brownell, Massachusetts General Hospital
Karin R. Corey, Memorial Hospital for Cancer and Allied Diseases
William H. Ellett, Royal Postgraduate Medical School, London

R. Eugene Johnston, Vanderbilt University
 Katherine A. Lathrop, University of Chicago
 John S. Laughlin, Sloan-Kettering Institute
 Robert Loevinger, International Atomic Energy Agency
 John McAfee, State University of New York
 Kenneth R. McCormack, Saroni Tumor Institute
 Richard Peterson, University of Iowa
 James S. Robertson, Brookhaven National Laboratory
 Robert H. Rohrer, Emory University
 Henry N. Wagner, Jr., The Johns Hopkins University
 Henry N. Wellman, Robert A. Taft Sanitary Engineering Center

Others who helped in the early stages were Robert Greenlaw, University of Kentucky; C. C. Harris, Oak Ridge; J. Krohmer, Roswell Park; G. Leudenblad, E. R. Squibb and Sons; and Jonathan Miller, Abbott Laboratories, who stayed on as secretary. As the work went forward, Smith became executive director; Rohrer, chairman; and Blau, vice-chairman. Ellett moved to Oregon State University. Walter Snyder of Oak Ridge, already the dean of Internal Dosimetry^(a) from the radiation protection standpoint, got interested and contributed greatly to the newer formulations, and Thomas Dillman of Ohio Wesleyan University (earlier Oak Ridge) joined up to bring his expertise in radionuclide decay schemes and nuclear parameters.

There can be no question about the breadth of representation in MIRD from the standpoint of both disciplines and institutions. Yet, key roles were obviously played by "old pros" such as Blau, Brownell, Loevinger, Robertson, Snyder, and Wagner, with Smith's enthusiastic leadership.

Abbreviated subjects and a list of the authors of the first nine pamphlets are given below. They are included in the references to this chapter.

Pamphlet

1. Schema; Loevinger and Berman (1968)
2. Energy Deposition in Water; Berger (1968)
3. Absorbed Fractions; Brownell, Ellett, and Reddy (1968)
4. Decay Schemes; Dillman (1969)
5. Absorbed Fractions; Snyder, Ford, Warner, and Fisher (1969)
6. Decay Schemes, Part 2; Dillman (1970)
7. Distribution of Absorbed Dose; Berger (1971)
8. Absorbed Fractions for Small Volumes; Ellett and Humes (1971)
9. Absorbed Dose from Radionuclides; Atkins, Robertson, Croft, Tsui, Susskind, Ellis, Loken, and Treves (1980)

Perusal of the titles for the first eight pamphlets indicates a depth of treatment of physical aspects quite beyond that expected from an enterprise trying to rectify only problems with medical aspects of dosimetry. It was a major research undertaking. There are those, and some are within the nuclear medicine fraternity, who feel that some of the effort was more for the promotion of nuclear medicine as a separate viable discipline than to solve the problems outlined in the prelude to the first pamphlets. But this does not detract from the validity of the system developed.

(a) Called "Mr. Internal Dosimetry" in his citation for the Distinguished Achievement Award of the Health Physics Society in 1975.

The ninth pamphlet concerns the specifics of radioxenons. Later pamphlets went back over some of the same ground and included detailed information for decay schemes for medically important radionuclides, the absorbed dose (S) per unit of cumulated activity for selected radionuclides, kinetic models, etc. Some of these were close to, indeed part of, the system described in the next section.

We will not cast judgment on whether or not it could have been done an easier way and the research talent applied elsewhere. Instead, let us look at the primary features of the MIRD system.

In a simplified version written by Cloutier, Watson, and Coffey (1978) for a text book of nuclear medicine, the MIRD formulation looks as follows:^(a)

$$\dot{D} = k \cdot \frac{A}{m} \cdot E$$

where \dot{D} = the absorbed dose per unit time
 k = a constant whose value depends on the units used for the other factors in the equation
 A = the amount of activity
 m = the tissue mass so that A/m is the activity per unit mass
 E = the average energy released per transformation.

If \dot{D} is expressed in rads per hour, A in microcuries, m in grams, and E in million electron volts per nuclear transformation, the constant k is 2.13 and the dose rate equation becomes

$$\dot{D} = 2.13 \frac{A}{m} E.$$

Because the average energy released per transformation, E , is a constant for each radionuclide, the two constants, k and E , may be combined into one constant, Δ .

$$\Delta = 2.13 E.$$

Hence,

$$\dot{D} = \frac{A}{m} \Delta.$$

In reality, a Δ value exists for each type of radiation: β^- , β^+ , γ , etc.

This concerns equilibrium absorbed dose for uniformly distributed radionuclides and a finite homogeneous medium (Δ is the equilibrium absorbed dose constant) and assumes there are no boundary effects. When the attempt is made to extend to general situations, a much more complex-appearing formulation is generated.

First we should consider the adoption of the absorbed fraction concept. This has already been alluded to and was used in some of the later versions of the classical scheme. However, it was applied in full for the MIRD formulation. Sometimes called the Loevinger-Berman formulation, it generalized from a formulation introduced into gamma-ray dose calculations by Ellett, Callahan, and Brownell (1964). It represents the fraction of the energy emitted in a source organ that is absorbed in the target organ. (Sometimes these may be one and the same, and the absorbed fraction is then 1.)

(a) Good, somewhat simplified descriptions of the MIRD scheme are given by Cloutier and Watson (1973), as well as by Cloutier, Watson, and Coffey (already cited), but those interested in the whole story must go to the MIRD pamphlets.

Single absorbed fractions are symbolized by d , while the specific absorbed fraction is defined as

$$\phi = \frac{\phi}{m}$$

Note that the specific absorbed fraction is simply the absorbed fraction per unit mass.

When all the components are put together, a single equation can be generated to cover dose or dose rate from any source of activity to any target for all types of radiation. Loevinger represents this as follows:

$$\bar{D}(r_1 \leftarrow r_2) = \bar{A}_2 \sum_i \Delta_i \phi_i(r_1 \leftarrow r_2) \quad \text{Upper arrow (3a)}$$

$$\text{Lower arrow (4a)}$$

The symbol \bar{D} indicates that the equation gives the mean dose. The argument of \bar{D} is $r_1 \leftarrow r_2$, which indicates that the mean dose is that given to target region r_1 from source region r_2 . Since the definition of a region includes points, lines, surfaces, and volumes, it follows that the equation applies to any source and any target. The left side of the equation can be read as "the mean dose to region r_1 from region r_2 ."

The symbol \bar{A}_2 represents the cumulated total activity in region r_2 during the relevant time interval. The activity A_2 , of which \bar{A}_2 is the integral, can be distributed in region r_2 in any manner, i.e., the equation does not assume a uniform distribution of activity in the source region. . . It is now apparent that \bar{D} is the spatial mean dose in the target region during the time interval over which the activity has been integrated.

Equation 3a is quite general, containing no assumptions about the distribution of the activity or the nature of the absorbing material. The term $\phi_i(r_1 \leftarrow r_2)$ can be read as "the specific absorbed fraction in target region 1 from source region 2." Although this equation is always valid, there may be some difficulty in obtaining numerical values for $\phi_i(r_1 \leftarrow r_2)$ for a nonuniform distribution of activity in the source region r_2 .

Equation 4a applies only when the reciprocity relation (originally due to Mayneord) is valid. Then the term $\phi_i(r_1 \leftrightarrow r_2)$ can be read as "the specific absorbed fraction in r_1 from r_2 , or in r_2 from r_1 ." The double-ended arrow in fact represents the entire reciprocity relation, which in its most general form simply says that the specific absorbed fraction is independent of which region is designated source and which is designated target. (Loevinger 1970)

After some further explanations, Loevinger goes on as follows:

We are now in a position to recognize that the general dose equation is not a forbidding and mysterious thing but is just a common-sense way of expressing the absorbed dose. To see this let us write Eq. 3a for a single radiation type:

$$\bar{D}_i(r_1 \leftarrow r_2) = \bar{A}_2 \Delta_i \phi_i(r_1 \leftarrow r_2)$$

Since Δ_i is the emitted energy per disintegration and ϕ_i is the fraction of this energy absorbed per unit mass in the target region, the product $\Delta_i \phi_i$ must be the i -type energy absorbed per unit mass per disintegration in the target region. Multiplying this product by the number of disintegrations, \bar{A}_2 , gives the i -type energy absorbed per unit mass in the target region, i.e., the mean dose from i -type radiation. To obtain Eq. 3a, it remains only to sum over all radiation types.

Thus we see that the concept of specific absorbed fraction allows formulation of a simple, easily understood equation which includes all possible sources and targets and radiations and which may exclude or include the reciprocity relation by a small change of notation (single-ended to double-ended arrow). Note particularly that this degree of generality was not possible until the specific

absorbed fraction was introduced. This one concept at a single stroke unified the entire field of internal-dose calculation into a single equation.

And later on the author states:

Equations 3a and 4a can, of course, be written in simpler forms for particular purposes. Certainly they appear much less forbidding if written simply as

$$\bar{D} = \bar{A} \sum \Delta_i \Phi_i$$

(Loevinger 1970)

Quite obviously, one does not undertake such generalized all-inclusive calculations with a simple old-fashioned desk calculator. Another prime contribution of the MIRD work was the use of the computer-based Monte-Carlo method. Whereas a manual method was possible as described by Snyder (in Morgan and Turner 1973, especially page 312) by utilizing "first-interaction" calculations with averages rather than probabilities, the Monte-Carlo system uses a scheme based on random numbers through which one can select a value of an indeterminate variable to use in a given calculation.^(a)

A final advance introduced by the MIRD approach was the very liberal use of phantoms to represent body organs or even the whole body at different ages. These are used both experimentally and as mathematical models. The experimental phantom is constructed of material that simulates living tissue in atomic composition (i.e., is tissue equivalent) and simulates also the shape, size, and relative location of body organs. Sometimes they are hollow plastic shells, which can be filled with a radioactive solution or with a discrete source, and measurements can be made at various distances and in different configurations. There are also models of each important organ. These go far beyond the convention of the classical system with its spherical model and with the radio-nuclide uniformly distributed therein.^(b,c)

The mathematical organ models are given in detail by Snyder et al. (1969) and Snyder (1970) and by Cloutier, Watson, and Coffey (1978). They look sufficiently like surrealistic paintings of the Salvador Dali school to make anyone feel very modern. But they have served their purpose well. The phantoms (models) for standard man and child are robot-like in appearance. The reference-man phantom, showing some internal organs, is presented well in the paper by Cloutier, Watson, and Coffey (1978) and is reproduced as figure 20.2.

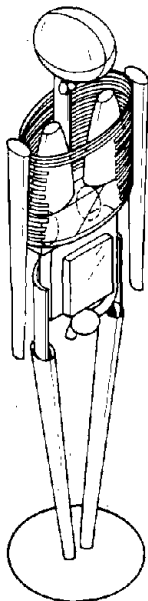


FIGURE 20.2. Reference-man phantom showing some internal organs. (Redrawn from Cloutier, Watson, and Coffey 1978. Reprinted with permission of Lea and Febiger, Philadelphia, Pennsylvania, copyright 1963.)

- (a) It is somewhat surprising that the introduction of this highly sophisticated, almost occult set of manipulations did not scare away the physicians. Evidently they were convinced not to flinch by the many other contributions of computer science to medicine.
- (b) Similar phantoms were used for years in x-ray dosimetry and could as well have been applied in the "classical ICRP" system for internal dosimetry. Indeed, they were to some extent.
- (c) Further details concerning these phantoms and models, especially the pediatric models, and including pictures as well as diagrams, appear in the NCRP report cited above (NCRP 1985c.)

Obviously, the MIRD schema introduced entirely different symbols for the key quantities, even those closely similar to the Marinelli-Quimby-Hine system. This has resulted in the MIRD system seeming more different from the classical one than it is. (The development of an entirely new symbolism seems to be irresistible to any committee engaged in developing a major revision of any system involving mathematical formulations.) The summaries by Cloutier and colleagues already cited give the details. Robertson (1981) has related the classical gamma dose formula to the MIRD formula by first expanding the various factors into their component parts and then regrouping them.^(a) He also points out those factors that are not interconvertible because they were developed by quite different methods. The doses calculated by the two methods are usually in close agreement, it may be added.

Before we consider further details, we should list a few of the advantages of the MIRD schema as enumerated by Loevinger:

1. It applies to all types of radiations without exception. As a result, no arbitrary categories are imposed on the radiation types.
2. It applies to all source regions and all target regions, i.e., to points, lines, surfaces, and volumes.
3. Dose and dose-rate equations are the same except for a simple change of symbols. The emitted energy per disintegration, Δ_i , depends only on the radionuclide considered.
4. The schema separates the physical and biologic factors in a clean and convenient manner. For the usual case, when the assumed organ size and distribution of activity do not change with time, the activity A (or the radioactive concentration C) contains all the time-dependent terms, such as the physical and biologic half-lives. The emitted energy per disintegration Δ_i contains not only the mean energy per disintegration but also the conversion factors for the chosen units. The specific absorbed fraction Φ_i (or the absorbed fraction ϕ_i) contains the information on the distribution of the absorbed energy from the source.
5. The absorbed fraction ϕ is often a convenient parameter. It is bounded by zero and unity, and, as a result, it is often possible to make a common-sense estimate of ϕ with adequate accuracy. The value of ϕ is insensitive to the size and shape of the target volume when $\phi \approx 1$. The ϕ 's add when combining target volumes.

These are but a few of the listed advantages. Loevinger goes on to say:

For some, one disadvantage of the method of internal-dose calculation that I am describing is its unfamiliarity. To become familiar with it, a person must devote considerable time to mastering it, and that time can be justified only if the new method offers significant advantages over the old. Obviously I believe this to be true because otherwise I would not presume to advocate the new method. (Loevinger 1970)

C. The Snyder-Modified ICRP System

The fact that Walter Snyder, Oak Ridge National Laboratory (ORNL), was enlisted into and became deeply interested in the MIRD enterprise, as mentioned earlier, brought about a very important confluence of the two systems. Snyder recognized that the deficiencies in the original classical system, outlined above, applied also to the calculations for radiation protection purposes and

(a) This maneuver by Robertson has as many arrows as a complex football-play diagram and attests to the extent of the differences. Nevertheless, the fact that it is possible indicates there are basic similarities.

occupational exposures. Over a period of several years, he and the Oak Ridge Internal Dosimetry group developed a very complete new system of dosimetry calculations using in part his contributions to the MIRD. Since he already had the data bank of physical and biological "constants" used for ICRP and NCRP reports and could modify them in the light of new information turned up in the MIRD activities, he could stimulate a comprehensive development. Colleagues in this enterprise were Mary Rose Ford, who has been identified with internal dosimetry since the time when K. Z. Morgan chaired the Internal Dose Committees of both ICRP and NCRP and who preceded even Walter Snyder into the field; Karl Morgan, especially in the decade of the sixties; John W. Poston, a bright young physical scientist at the Georgia Institute of Technology;^(a) G. G. Warner, S. B. Watson, S. F. Deus, and V. Provenzano, all at ORNL at the time. Associated, but more or less independent, was S. R. Bernard, ORNL.

Some of this work went in parallel with the developments of Ellett and coworkers in the MIRD enterprise, already cited. (Representative references are: Snyder and Ford 1965; Snyder, Ford, and Warner 1968; Snyder et al. 1975a,b,c; Snyder, Ford, and Watson 1975; Snyder et al. 1976; Snyder 1970; Ford, Snyder, and Warner 1975; Deus and Poston 1976; and Deus, Provenzano, and Snyder 1977.)^(b)

A corollary to the absorbed fraction as used in MIRD is an entity derived from it and applicable to the final results called the "S" value. This was introduced by Snyder and perhaps the "S" can be traced to his name. It represents the absorbed dose per unit of cumulated activity, i.e., rad/ μ Ci-hour.

Since this system was much more likely to be applied to materials of long physical and/or biological half-lives than the MIRD system, factors for retention kinetics were necessary. It was possible to utilize the long experience with radioisotopes in the body and introduce retention equations with much more than a single exponential. These could be tailored to the period over which the calculation was desired and worked into the concept of dose commitment described by the ICRP (ICRP 1979) as related in chapter 16 and commented upon by NCRP (1985a).

The system was developed to apply more to radiation protection activities than to medical doses as such and to this extent works best for a population of adults. Inaccuracies will occur if it is applied to individual patients whose physical and physiological characteristics may differ from the models and phantoms used. Since it is unrealistic to construct a special phantom for each patient, a system of scaling factors has been started, but it is clear that such a system cannot be simple.

The result can be seen as ICRP Publication 30 (1979) and its voluminous appendices which give "S" factors and other derived figures such as annual limits for intake and derived air concentrations for over seven hundred radionuclides and a large variety of source and target organs. (The NCRP is now busy adapting the main features of the system to U.S. practices; see NCRP 1985a.)

(a) At Oak Ridge in the earlier years and moved recently to Texas A&M University.

(b) The assembly of these and many other references used in this section was aided greatly by use of a draft NCRP report prepared by J. S. Robertson (formerly Mayo Clinic, now DOE) and NCRP Scientific Committee-55, recently published as NCRP report No. 83 (NCRP 1985c).

Since this was all an outgrowth of the activities of Snyder and his associates, it seems appropriate to call the system the "Snyder-Modified ICRP System" or "Snyder System" to honor Walter Snyder's memory.

The work has been carried forward since Dr. Snyder's untimely and unfortunate death in 1977 (for obituary see *Health Physics*, Vol. 34, No. 1, January 1978) by many of his former associates, particularly Troyce Jones, John Poston, and, of course, Mary Rose Ford, and by more recent additions, J. M. L. Hwang and Keith Eckerman.

Comment. The MIRD and Snyder Systems can be regarded as major contributions of nuclear medicine to radioisotope toxicology to the degree that standard setting and radiation protection are closely related to the toxicology enterprise and also as an interaction in the other direction.

Yet, the task is far from completed. On the nuclear medicine side, it is frequently necessary to idealize the patient and his health status to an undesirable extent. We need easier ways to go from the general to the specific. (Desk-top computers in nuclear medicine departments are already beginning this.) We still need much more information on the true spatial distribution of radionuclides within source organs. We are still undecided about the true target cells in many situations and will be until the mechanisms of carcinogenesis and other biological processes are further elucidated.

On the radiation protection side, we have less reason to tailor the calculation to a particular individual except for evaluation and assessment of significant over-exposures. But we are in need of much better models for different ethnic groups, different age groups, and the effect of physiological and biochemical abnormalities. We have only one fully developed model for metabolism of radioisotopes in a tissue, viz., bone, as seen in chapter 16.

Naturally, the nuclear medicine people usually find the MIRD system appealing, especially because of the assemblage of data covering radiopharmaceuticals and thus direct pertinence to their operations. For the same reason, most workers in radiation protection use or plan to use, with modifications, the Snyder-Modified ICRP scheme. Yet, some workers in nuclear medicine—not necessarily old conservatives—lean toward the classical system, while many health physicists teach and use the MIRD system.

The extent to which the final answers obtained by the two systems are comparable was illustrated by Snyder (1973) with estimates of absorbed fractions. He compared the manual ICRP (the classical ICRP not the Snyder-Modified ICRP) and the Monte-Carlo methods. The results are shown in table 20.1.

The figures are not identical and show a progression in their ratio from about 0.9 to 1.39 (ICRP/Monte Carlo) with increase in energy. The larger differences, almost 40%, occur in high-energy regions of more application to radiation protection and toxicologic dose calculations than to medical uses. The final answers are not changed as much as these absorbed fractions.

It is obvious that the efforts put into internal dosimetry have been of considerable magnitude and involved much research talent. They have occupied some excellent minds full-time and a gifted cadre of people who were good at calculations and later at computer operations, and who could also sift an enormous mass of physical and biological information to insert the best estimates for a given function (chapter 16).

Despite the considerable input from the nuclear medicine side, a large share of the daily sweat came from the brows of people supported in the major

TABLE 20.1. Estimates of the Absorbed Fraction for Total Body (70 kg)

E _x (MeV)	ICRP	Monte Carlo	ICRP/Monte Carlo
0.040	0.812	0.861	0.94
0.080	0.532	0.593	0.90
0.160	0.575	0.513	1.12
0.364	0.632	0.499	1.27
0.662	0.636	0.481	1.32
1.46	0.586	0.434	1.35
2.75	0.504	0.362	1.39

Source: Reset from Snyder 1973. Reprinted with permission of Krieger Publishing Company, Melbourne, Florida, copyright 1973.

internal emitter toxicology groups—on both sides of the Atlantic—whom we have met earlier in this book. Thus, the effort must be set down as an important product of governmental support for both the experimental and computational programs. We would have no decent standards or proper medical controls without them. A glance at the absorbed doses from current nuclear medicine procedures given in the cited NCRP report (NCRP 1985c, Table 1.1) attests to the effectiveness of the vigilance in both the nuclear medicine and radiation protection sectors, toward keeping the radiation doses low.

III. Effects at the Cellular Level^(a)

A. The Setting

This is a unique chapter in our field of interest. In chapter 10, we noted that many of the substances used in tracer chemistry and nuclear medicine involved the presence of radionuclides placed in the precursors of nucleic acid synthesis or other important building blocks for cellular metabolism and growth. Many of these have been used primarily in cellular radiobiology where tritium-labeled, iodine-labeled, or carbon-labeled DNA or RNA^(b) precursors have been applied extensively to unravel the basic mechanisms of cell growth and division and to identify the principal target molecules for radiation damage. In such instances, the labeling activity is limited to what is needed to provide good measurements. The site of localization can be handily determined by the application of sophisticated autoradiographic methods. The work began late in the 1950s in many laboratories of cellular radiobiology and molecular biology. It contributed much to our knowledge of the origins and development of the important cell populations from the original "stem cells." One of the earlier

(a) Obviously, the genesis of nearly all effects we have been discussing is at the level of the individual living cell. However, the results are most frequently expressed primarily in more complex integrated systems involving organs or tissues. In this section, we are concerned with events that not only begin at but are expressed primarily at the cellular level of organization.

(b) Ribonucleic acid.

examples, from Quastler and Sherman (1959) working at Brookhaven and Brown University, concerned cell population kinetics in the intestinal epithelium of the mouse. Labeling was done with either ^{32}P or ^3H ; the former as the phosphate, the latter in thymidine. Good early summaries of the usefulness of the tracer-level work are given by Hughes et al. (1958), Bond et al. (1959), and by Cronkite et al. (1962) primarily at Brookhaven. A few of the administrations were to humans.

A parallel development involved higher than tracer-level activities and was directed at the overt production of effects, especially cell "killing"^(a) under a variety of circumstances.

We wish here to examine the toxicologic overtones of the tracer uses and the toxicologic findings at the higher activity levels.

B. Uses to Establish Mechanisms

Radionuclides that could be synthesized into biologically important molecules, especially the nucleic acid and protein precursors underlying cell growth and development, were used in two major ways: (1) primarily as tracers, and (2) as carriers of radioactivity into these primary structures. The latter is a unique application of the toxicology of radionuclides, since it has been used extensively to unravel the mechanism of cell killing by radiation. Both constitute most important and scientifically useful facets of the story of the radionuclides.

The tracer level work contributed to two very different problems. First was its application to tracing the growth and differentiation of major cell lines. The origin of many cells (especially those involved in blood formation, but also germ cells, antibody-producing cells, malignant cells, and nearly all other cells that turn over rapidly) had been most difficult to work out by morphological techniques alone. The advent of labeled compounds, which would enter the cycles of growth and development and could, moreover, produce clear autoradiograms without undue radiation dose to the cell, was a major advance. Excellent vignettes of the techniques and results can be found in volume 2 of the International Atomic Energy Agency (IAEA) publication, *Tritium in the Physical and Biological Sciences*. The review by that stellar hematologist Eugene Cronkite and his colleagues from Brookhaven is especially complete (Cronkite et al. 1962). (Obviously, other synthetic processes, such as synthesis of DNA [Bianchi, Crathorn, and Shooter 1962] could be studied also.) A glimpse of the work with microorganisms can be seen in Painter, Forro, and Hughes (1958) working at Brookhaven and Yale.

The second tracer use was to mark the sites in dividing cells where radiation damage might be occurring.

While tritiated thymidine has now been used in nearly every laboratory interested in cellular radiobiology, the work started at Brookhaven National Laboratory (Taylor, Woods, and Hughes 1957),^(b) and the group there has remained

(a) Although it became customary to call the effects "cell killing" and the quantitative relationships "survival" curves, the process was really inhibition or prevention of cell division and growth, i.e., it was a reproductive death. Such cells might continue to live as "resting" cells.

(b) Also in Belgium independently by Verly and Hunebelle (1957).

active ever since.^(a) As the work progressed and the collaboration of the synthetic chemist and the molecular biologist became ever more fruitful, many other nucleic acid precursors were labeled (e.g., cytosine). The autoradiographic technique has been a powerful tool in depicting the cellular localization of these substances (Taylor 1962; Maldague, Que, and Maisin 1962; Schultze and Maurer 1962; and Woods 1962).^(b)

The use of higher activity levels to produce cell killing in specific systems began at Washington University, St. Louis, spread to Brookhaven and later throughout the scientific community interested in identifying the major targets for radiation damage. Such work was largely responsible for proving that it is the intracellular DNA that is the primary target in the radiation death of cells in reproduction (Okada 1970).^(c)

Much work with the higher activities involved an experimental technique called the "Suicide Experiment" (Okada 1970, p. 99 and pp. 121-132) or, as some prefer to call it, "cytocide." Hershey and colleagues (1951) at Washington University first developed the procedures. Cells are labeled by culturing them with a radioactive precursor of DNA or RNA. After sufficient time for the precursor to enter the growth mechanisms, the cells are cooled (frequently to -196°C). This stops all metabolic processes. However, the decay of the radioactive atoms continues, since this is a physical process and is independent of temperature. After allowing time for a calculated number of decays, and thus a desired radiation dose, to accumulate, the cells are warmed back to 37°C , and their further growth and division are followed. In addition, subsequent phenomena, such as mutations, chromosome aberrations, ability to perform certain specific synthetic processes, are measured. With suitable choice of precursors and observation by autoradiography, relatively precise information can be obtained on the site and kinds of damage produced.

The early work in this field used ^{32}P as well as tritiated nucleic acid precursors and organisms ranging from single-stranded viruses to mammalian cells. A useful summary of the earlier key experiments can be found in table 20.2, taken from Okada (1970, pp. 128-129).

(a) We saw some of the Brookhaven work in chapter 10. Other major contributors to this cell-level work, all of it in post-World-War-II years with major developments in the decades of the late 1950s and 1960s, were located at: Argonne Cancer Research Hospital; Argonne National Laboratory; Biology Division, Oak Ridge National Laboratory; Colorado State University (Ft. Collins); Columbia University; Donner Laboratory at the University of California, Berkeley; Laboratory of Radiobiology, University of California at San Francisco; M. D. Anderson Hospital, Houston; Ohio State University; Pennsylvania State University; University of Rochester; Washington University, St. Louis. In later years, these were joined by efforts ranging from major to supplemental at nearly every large institution engaged in nuclear medicine and molecular biology. There was, of course, much work abroad, particularly in England and West Germany.

(b) Taylor was at Columbia University; P. S. Woods at the University of Delaware; Maldague and colleagues at Louvain, Belgium; and Schultze and Maurer at the University of Cologne. Thus, we gain an idea of the rapid spread of these techniques and studies and their almost ubiquitous occurrence. Remember, too, that this is a mere sampling of the literature.

(c) Okada worked at Rochester for a number of years and wrote his major monograph while a staff member in radiation biology and biophysics.

TABLE 20.2. Efficiency of Killing of Organisms—"Suicide Experiments"

Classification	Organism	Radioactive Atom	Storage Conditions	Efficiency of Killing (α)	N ^{a,c}	Reference ^a
Single-stranded viruses	Φ X174 phage	³² P	4°C	1.1	DNA	1
	Φ X174 phage	³² P	-196°C	0.94	DNA	2
	S13 phage	³² P	4°C	1.1	DNA	1
	S13 phage	³² P	-196°C	0.94	DNA	2
Double-stranded DNA viruses	T2 phage	³² P	b	0.12	DNA	3
	T2 phage	Thymine-5'- ³ H	4°C	0.13	Phage	4
	T2 phage	Thymidine-5'- ³ H	4°C	0.14	Phage	4
	T2 phage	Thymidine- ³ H	4°C	0.14	Phage	4
	T4 phage	³² P	-	0.122	DNA	3
	T3 phage	³² P	-	0.130	DNA	3
	T5 phage	³² P	-	0.155	DNA	3
	T7 phage	³² P	-	0.191	DNA	3
	λ phage	³² P	-	0.150	DNA	3
	<i>E. coli</i> B/r	³² P	-196°C	0.02	DNA	1
	<i>E. coli</i> 3000	³² P	-196°C	0.02	DNA	5
	<i>E. coli</i> B ₃	³² P	-196°C	0.026	DNA	6
Bacteria	<i>E. coli</i> B/r	³² P	-196°C	0.033	DNA	8
	<i>E. coli</i> B ₃	³² P	-196°C	0.029	DNA	10
	<i>E. coli</i> B ₃	³² P	-196°C	0.0275	DNA	10
	<i>E. coli</i> 15T-L ⁻	Thymidine- ³ H	4°C	0.029	Bacteria	7
	<i>E. coli</i> 15T-L ⁻	Thymidine- ³ H	-78°C	0.012	Bacteria	7
	<i>E. coli</i> 3000	Thymidine- ³ H	-196°C	0.0033	Bacteria	5
	<i>E. coli</i> B ₃	Thymidine- ³ H	-196°C	0.0047	DNA	9
	<i>E. coli</i> CB13	Thymidine- ³ H	-196°C	0.00058	DNA	9
	<i>E. coli</i> B ₃	Thymidine- ³ H	-196°C	0.00052	DNA	6
	<i>E. coli</i> B ₃	Thymidine- ¹⁴ C	-196°C	0.0135	DNA	6
	<i>E. coli</i> 3000	Uridine- ³ H	-196°C	0.0025	Bacteria	5
	<i>E. coli</i> 15T-L ⁻	Uridine- ³ H	4°C	0.015	Bacteria	7
	<i>E. coli</i> 3000	Leucine- ³ H	-196°C	0.0011	Bacteria	5
	<i>E. coli</i> 15T-L ⁻	Histidine- ³ H	4°C	0.011	Bacteria	7
	<i>Salmonella typhimurium</i>	³² P	-20°C	0.012	DNA	11
	<i>Aspergillus nidulans</i> (haploid spore)	³² P	5°C	0.018	DNA	19
	<i>D. pneumoniae</i>	³² P	-20°C	0.04	DNA	12
Yeasts	Diploid	³² P	-4°C	0.0089	DNA	18
	Haploid	³² P	-0°C	0.01	DNA	13, 14
Mammalian cells	D98/AG	³² P	-70°C	0.00025	DNA	15
	KB	³² P	-196°C	0.0004	DNA	16
	LS178Y	Thymidine- ³ H	-196°C	0.006	Cell	17

^a Key to references:

- G. S. Stent, and C. R. Fuerst, *Advan. Biol. Med. Phys.* 7, 1 (1960).
- I. Tessman, *Virology* 1, 263 (1959).
- D. T. Denhardt, and R. L. Sinsheimer, *J. Mol. Biol.* 12, 663 (1965).
- J. Cairns, *J. Mol. Biol.* 3, 756 (1961).
- M. Rachmeter, and A. B. Pardee, *Biochim. Biophys. Acta* 68, 62 (1963).
- S. Apelgot, and R. Latarjet, *Biochim. Biophys. Acta* 55, 40 (1962).
- S. Persons, *Biophys. J.* 3, 183 (1963).
- F. Kaudewitz, W. Vielmetter, and H. Friedrich-Freska, *Z. Naturforsch.* 13b, 793 (1958).
- S. Apelgot, *Intern. J. Radiation Biol.* 10, 495 (1966).
- S. Apelgot, and R. Latarjet, *Intern. J. Radiation Biol.* 10, 165 (1966).
- Y. Yan, and S. Kondo, *Radiation Res.* 22, 440 (1964).
- M. S. Fox, *J. Mol. Biol.* 6, 85 (1963).
- E. Moustacchi, *Biochim. Biophys. Acta* 36, 577 (1959).
- E. Moustacchi, and H. Marcovich, *Ann. Inst. Pasteur* 103, 841 (1962).
- G. Ragni, and W. Szybalski, *J. Mol. Biol.* 4, 338 (1962).
- F. R. Leach, *Proc. Soc. Exptl. Biol. Med.* 115, 665 (1964).
- H. J. Burki, and S. Okada, unpublished data (1968).
- J. Drobnik, *Radiation Res.* 21, 339 (1964).
- P. Strigini, C. Rossi, and G. Sermoni, *J. Mol. Biol.* 7, 683 (1963).

^b Not described.^c N^a is the number of radioactive atoms expressed per DNA or per organism (phage, bacteria, and cell): (a)(a) While this is verbatim from the original, obviously this column supplies no numbers. Instead, the designation given signifies the entity (DNA or organism) interacting for the quantity N^a.

Source: Reser from Okada 1970. Reprinted with permission of Academic Press, Orlando, Florida, copyright 1970.

The "efficiency of killing" (α) is derived from the classical equation relating survival (i.e., ability of a cell to divide) and radiation dose. Fortunately, most of the relations are exponential (or can be handled as exponentials). Thus:

$$S = S_0 e^{-\alpha D}$$

where S_0 = original number of living organisms

S = the fraction of organisms surviving after decay of a stated number of radioactive atoms

D = dose

α = efficiency of killing

Table 20.2 indicates the high efficiency of ^{32}P in the very simple systems. The near unity α figure for killing of a single-stranded DNA virus by ^{32}P means that decay of one radioactive atom is enough to disable the system. The needed number of disintegrations naturally increases in progression to double-stranded viruses and on to more complex systems like bacteria, yeast, and mammalian cells, which have more units requiring disabling before cell division is inhibited. Many variations occur as a function of strain of cell, heterogeneity of the cell population, stage in DNA replication, amounts of DNA per cell, etc. However, the principle has been established.

It will be noted that the efficiency of killing of mammalian cells by ^{32}P decay is considerably less than that for tritium. This could mean a greater efficiency of the very localized radiation of tritium compared to ^{32}P . Okada (1970, pp. 129-130) cites other possible reasons for the difference.

The importance of chemical factors, or at least the chemical nature of the carrier of the radioactivity, can be seen in an important paper by Burki and Okada (1968).^(a)

They found that the killing efficiency of tritium was markedly reduced when it was attached to uridine, which labels RNA rather than DNA, or when it was attached to histidine or lysine, which placed the radioactivity in the so-called acid-soluble rather than the protein fraction. By a maneuver that placed the label in the cytoplasm rather than the nucleus, they also found a decrease in efficiency. When the suicide technique was applied to other cellular effects besides reproductive death, it was also found that the nature of the precursor played an important role, and it was different from that in reproductive death. This was particularly noticeable in the induction of mutations in bacteria (*E. coli*) (Person, Snipes, and Krasin 1976).

These experiments enabled estimation of the size of genes and, perhaps most importantly, demonstration that the killing efficiencies for reproductive cell death followed the same progression as the ratios of calculated target volume divided by the DNA content of the organisms. This applied when similar calculations were made using x-rayed cells and could be used as proof that DNA is likewise the target for radiation-induced inhibition of cell division by external radiation.

(a) This work came from the Division of Experimental Radiology at the University of Rochester and the Donner Laboratory at Berkeley. Dr. Burki received his doctorate under the direction of Okada and went ahead to carve out an important career in cellular radiobiology at Berkeley. His untimely death in midcareer leaves a significant amount of work undone, as well as much good work completed.

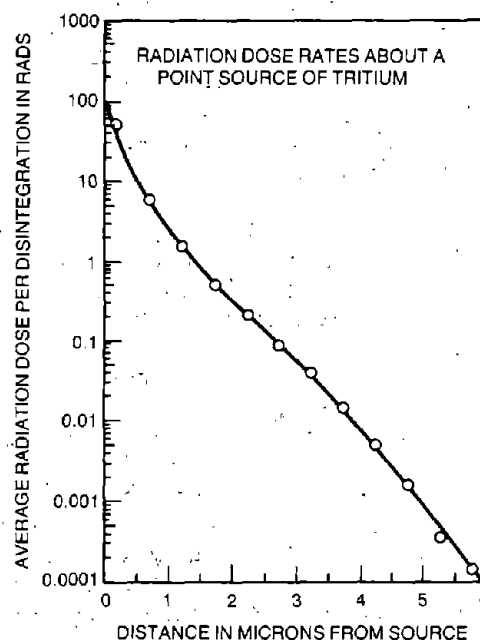
C. On the Radiation Dose to the Cell Nucleus

Since the radiations involved in some of these experiments were of very short range, it seemed doubtful if the doses associated with the phenomena just described could be calculated correctly by the conventional system, since this used an average dose over a volume much larger than a single cell or its nucleus.

Again, the first serious approach seems to have come from Brookhaven. At the first National Biophysics Conference held in Columbus, Ohio, March 4-6, 1957, J. S. Robertson and W. L. Hughes presented a paper that developed from their recent success in localizing high-specific-activity tritium by micromapping techniques within cell nuclei.^(a) In this milestone paper, Robertson and Hughes (1959) deduced that a single disintegration of tritium delivers a dose averaging 53.5 rad to an inner sphere 0.5 μ in diameter and 5.8 rad to the next 0.5- μ shell. This is not the dose to the cell nucleus, since most cell nuclei are several microns in diameter. More than one disintegration of tritium would be needed to apply this dose to a whole nucleus. However, the potential for selective radiation of even parts of the nucleus is apparent, a powerful tool when combined with localization by autoradiography.

Obviously, if the tritium is deposited as a single point source, the dose will fall off rapidly with distance, as shown in figure 20.3, taken from the paper by Robertson and Hughes.^(b)

FIGURE 20.3. Radiation dose rates about a point source of tritium. (Redrawn from Robertson and Hughes 1959. Reprinted with permission of Yale University Press, New Haven, Connecticut, copyright 1959.)



(a) As we have already seen, this resulted in selective irradiation of cell nuclei and of the DNA, which is found only in chromosomes, with relatively low radiation dose to the cell cytoplasm.

(b) It seems likely that this work began James Robertson's life-long interest in radioisotope dosimetry. He continued at Brookhaven for many years and made important contributions there. After his move to the Mayo Clinic, where he was a consultant in nuclear medicine, he had much influence on the MIRD developments, as we have already seen. He has also chaired or participated on many national committees with dosimetric charters or overtones. For example, he currently chairs the NCRP scientific committee charged with the experimental verification of internal dose calculations (NCRP 1985c). Still more recently, he joined the Headquarters staff of DOE and chaired the MIRD Committee in 1985.

This work ties in with the general problems of discrete radioisotope sources that we saw as the "hot particle problem" in chapter 9. It also relates to, but is on a different scale from, true microdosimetry as espoused by Harold Rossi and his colleagues at Columbia University, and many others (see, for example, Rossi 1967, whose work is at a still more micro level).

Robertson and Hughes were joined by Bond, Johnson, and Cronkite, among others, from Brookhaven and by Ludwig E. Feinendegen, who was headquartered at the Institute for Medicine in Jülich, West Germany, but who spent considerable time with the Brookhaven group to expand cellular-level dosimetry and to do experiments bearing on the effectiveness of the doses delivered by the various pertinent radioisotopes.

A paper by Bond and Feinendegen (1966) was a second milestone on the subject from Brookhaven. It used as a model bone marrow cells from a rat that had received $1 \mu\text{Ci}$ of ^3H - TdR per gram of body weight. They determined radioactivity levels radiochemically and autoradiographically. Using the average nuclear diameter as 8μ and the corresponding mass as 270 pg ,^(a) they calculated an average dose rate of about 8 rad per day to the nucleus. (Note that this is the average dose from tritium given at the level of $1 \mu\text{Ci}$ per gram of body weight and thus involves more averaging than the point source calculation of Robertson and Hughes.)

A third milestone paper from Brookhaven on the subject of dose to the cell nucleus came from Johnson in work described at the 1969 Oak Ridge symposium on medical radionuclides (Johnson 1970). By this time, the possible extra effectiveness of sources such as the tritium beta particle within cell structures was causing much consternation among those charged with radiation protection. Did we have a Trojan horse in our midst? Extrapolations were made by some, quite unreasonably, from the situation where the radioactivity was entering already incorporated in important biomolecules to situations such as the entry of tritiated water, even tritium gas, which we looked at in chapter 10. It was forgotten that only a small fraction of the radioactivity entering in these ways reaches dividing cells. The Johnson paper clarifies much of this.

Johnson adopted a two-pronged approach, calculation of dose and direct experimental comparison of the effects of a given calculated dose from tritium with the same dose from external high-energy radiation.

For the calculation, Johnson accepts the basic figures derived earlier but hastens to point out some of the complications. For estimation of nuclear dose associated with the biological effects produced, Johnson reviewed experimental work on mutation, chromosome aberrations, cell killing both *in vitro* and *in vivo*, tumor induction, and animal mortality. Although many of the dose estimates are quite approximate, the general conclusion could be drawn that the yields of effects from intracellular tritium were reasonably near to those expected from the dosage calculations. Thus, for the killing of mammalian cells *in vivo*, it appeared that calculation of absorbed dose to the nucleus from ^3H - TdR on the basis of energy absorbed per mass of nucleus gave a reasonable picture of expected effectiveness. In other words, no special factor needed to be introduced, even though the energy was absorbed almost entirely within the target molecule. (This does not mean equal effectiveness of an average whole-body dose for external radiation compared to ^3H - TdR, only comparability of

(a) This is now defined as the "reference nucleus."

absorbed doses in the quite radiosensitive structures we are dealing with. Effectiveness of a given dose in the nucleus may be well above that of the same dose averaged over the body. Indeed, the average dose to tissue is probably meaningless for substances incorporated into the cell nucleus.)

This paper led Allen Brodsky, who was then at the University of Pittsburgh, to deliver a eulogy on the virtues of tritium, as part of the discussion following Johnson's paper (1970). It is reproduced below.

BRODSKY: "Bravo" to Dr. Johnson's paper on tritiated thymidine. I have felt for some 9 to 10 years, since investigating the problems of tritium released to the environment, that tritiated thymidine was no more than about 100 times more radiotoxic than HTO. Even a factor of 100 increase in relative radiotoxicity per microcurie, based on a calculated dose rate to the genetic material, would still not put tritiated thymidine very high on the relative radiotoxicity scale. The relative ease with which tritium may escape into the environment has often been cited to indicate that tritium is a "hazardous" nuclide. However, in many research laboratories not enough tritium is handled at any one time to constitute a real hazard even in thymidine form. Furthermore, in estimating the hazards of tritium dispersed to the environment, he concluded that the probability of genetic mutation from ^3H transmutation to ^3He (assuming every transmutation deleterious) was even lower than the probability of radiation genetic mutation produced by the average beta dose to tissue fluid. This seems to agree with experimental results. So I would like to raise the flag again and say, 'Hail tritium.' It is God-given to us as the safest nuclide to use for these purposes.

(Brodsky 1970)

This statement cannot help but indicate how the worry that the possibility of a "special effect" had become imbedded in the biomedical community. It is of special interest since it came from one who is not prone to unbridled fits of enthusiasm.^(a)

Before leaving the subject of dose calculation to the cell nucleus, we should examine a useful summary table assembled from many sources by a committee of the NCRP chaired by Eugene P. Cronkite at Brookhaven. Taking a reference nucleus as defined earlier and the radiation distribution as either random *in the tissue as a whole* or random *within the reference nucleus*, factors were arrived at to convert disintegrations of a given radionuclide to absorbed dose in rad. They are shown in table 20.3, taken from the NCRP report (NCRP 1979).^(b)

The difference between a "within the nucleus distribution" and a "within the tissue distribution" is frequently quite large. Only with tritium (table 20.3) is the difference only on the order of 20%. Obviously, the higher the energy and the greater the range of the beta particles, the greater will be the dose to the nucleus from *outside* and the lesser the dose from *inside* if there is generalized distribution. Even tritium, however, loses a little energy from the nucleus by the "edge effect." Iodine-125 is a special case, which has the highest average

(a) As we shall see shortly, Brodsky's factor of one hundred may even be too high.

(b) Other members of this committee and their host institutions at the time are: Edward Alpen, Donner Laboratory; Michael Bender, Brookhaven; James Cleaver, University of California, San Francisco; Ludwig Feinendegen, Jülich, West Germany; Marylou Ingram, University of Miami; H. A. Johnson, Tulane (formerly Brookhaven); Frank Lowman, Environmental Research Laboratory of the Environmental Protection Agency; Eugene Oakberg, Oak Ridge National Laboratory; Stanley Person, Pennsylvania State University; and Edward Powers, University of Texas, Austin.

TABLE 20.3. Factors Used to Convert Disintegrations to Average Absorbed Dose in the Reference Nucleus

Radionuclide	\bar{E}_β keV	Average Absorbed Dose (rad) per Decay in Reference Nucleus	
		For Random Distribution in Tissue	For Random Distribution in Nucleus ^a
³ H	5.7	0.34	0.27
¹⁴ C	49.3	2.95	0.19
³² P	695.	41.5	0.04
³⁵ S	48.8	2.92	0.19
¹²⁵ I	19.6	1.17	0.71
¹³¹ I	195.	11.6	0.11

^a Corrected for loss of energy from the reference nucleus. The NCRP is indebted to M. J. Berger of the National Bureau of Standards, for the calculations needed to produce this table.

Source: Reset From NCRP 1979. Reprinted with permission of the National Council on Radiation Protection and Measurements, Bethesda, Maryland, copyright 1979.

absorbed dose in the nucleus, even though it is more energetic than tritium. This is because the energy appears as Auger electrons. (More about ¹²⁵I in a following section.)

D. Effects and Relative Effectiveness

The crescendo of work on biological effects and the relative effectiveness of different radionuclides and of different vehicles for bringing the radioactivity into the cell can only be hinted at in the space at our disposal. Much of it is at the heart of cellular radiobiology and has been fully reviewed by others. Yet, a few key findings and the trends of the work require attention. We will organize the review on a more or less chronological basis.

Obviously, the "suicide experiments" were effects studies, and many go back as early as 1959 (table 20.2). However, these were so focused on mechanisms that we preferred to discuss them as a separate entity rather than in this section concerning general effects.

Among the early general effects studies was work by the Brookhaven group on mouse spermatogonia. Johnson and Cronkite (1959) chose mouse spermatogonia as an early indicator of the effectiveness of intranuclear tritium because of their demonstrated great radiosensitivity (LD₅₀ of only 20 to 25 r of ⁶⁰Co 1.25-MeV gamma radiation). They chose doses of 0.5, 1, 5, 10, and 20 μ Ci/g body weight of tritiated thymidine and gave them intraperitoneally. On the whole, the effectiveness was low. Doses under 1 μ Ci/g (a sort of dividing line above which effects might be expected) were equivalent to less than 2 r of gamma radiation per day. A later report (Johnson and Cronkite 1967) continued to show low effectiveness at 5 as well as 1 μ Ci/g body weight.

There was also much work at Brookhaven on plant material such as root systems in *Zea Mays*, on *Tradescantia* (the liverwort), on the blue-green alga

Chlorella, and others. A good summary of the Brookhaven and other work was made available fairly early by Wimber (1964), who soon after went from Brookhaven to the University of Oregon. Wimber emphasizes the need for further extension of the studies, even though at that early date he could present a summary table with forty-five entries and organisms ranging from bacteriophage and bacteria through simple plants and plant root systems to rats, mice, and human cells in tissue culture. (Since the reference is readily available, the table will not be reproduced here.) The effects were inhibition of root growth and of cell growth, chromosome breakage and aberrations, various morphological changes in cells, tumor induction, and mutations.

Brooks et al. (1976) in collaborative work from Brookhaven and the Lovelace Foundation Inhalation Toxicology Research Institute studied the effects of continuous intake of tritiated water on liver chromosomes in mice. The experiment ran out to seven hundred days. They used the standard technique of a partial hepatectomy to stimulate liver cell division and maintained the animals at a level of $3 \mu\text{Ci}/\text{ml}$ in the drinking water. There was a higher level of chromosome damage in the treated animals, but it was difficult to establish statistical significance. It appeared that the effectiveness of the tritium beta particle was comparable to other beta-gamma emitters on a per-rad basis.

The group at ANL reported the induction of tumors in mice by radioactive thymidine, first in rather preliminary reports in 1961 and 1962 and then in 1966 in a definitive study (Baserga, Lisco, and Kisielewski 1966). This work was the first to demonstrate tumor production by tritiated thymidine. They gave tritiated thymidine to embryonic, newborn, two-month, six-month, and twelve- to fourteen-month-old mice in doses ranging from 0.1 to $10 \mu\text{Ci}/\text{g}$ body weight. They also administered thymidine labeled with ^{14}C rather than ^3H .

First, there was a marked difference in effectiveness between ^{14}C - and ^3H -labeled thymidine. No increase in tumor incidence was seen with the ^{14}C (in newborn at levels from 0.02 to $2.0 \mu\text{Ci}/\text{g}$ body weight), except for a statistically significant increase of lymphomas at the highest dose. By contrast, the ^3H -thymidine increased the incidence of rare tumors and accelerated the incidence and increased the total number of tumors of more frequently observed varieties. In considering mechanisms, the authors note that, while the biological half-life of tritiated water is only twenty-four to thirty-six hours, the tritium incorporated into DNA remains until the death of the cell or its dependents. However, only 10% of injected thymidine gets incorporated into DNA, and the amount present decreases with time as labeled cells divide and some are eliminated from the body. This bespeaks some form of multiplicative mechanism in the carcinogenesis, although the long retention of the radioisotope and relatively high initial dose may be sufficient in themselves.

The lack of effectiveness of ^{14}C -labeled thymidine is readily explained by the dosimetry. With the average range of the ^{14}C beta particle in tissue at about 10μ , much of the energy is dissipated outside of the cell nucleus.

At about the same time, the Brookhaven group compared the leukemogenic effect of ^{60}Co 1.25-MeV gamma radiation with ^3H -thymidine and ^3H -cytidine using mice. A preliminary report appeared in 1963. Only the mice receiving ^{60}Co gamma irradiation developed thymic lymphomas. Even by 1967 things did not change very much, despite a much larger experiment. The mean life spans and age-specific mortality rates in animals receiving 1 to $5 \mu\text{Ci}/\text{g}$ of tritiated thymidine or 400 R of gamma radiation were indistinguishable from those of control animals (Johnson and Cronkite 1967).

Meanwhile, at the M. D. Anderson Hospital in Houston, Dewey and colleagues compared tritiated thymidine, tritiated water (HTO), and ^{60}Co gamma rays for effectiveness in producing chromosome aberrations in cultured cells from the Chinese hamster (Dewey, Humphrey, and Jones 1965). The irradiation times in this in-vitro system were from ten to twenty-three hours. If any special effect of the radiation borne in by the nucleic acid precursor exists, it should turn up in a comparison of this sort. Instead, the energy absorbed in nucleus or chromosome from the ^3H - TdR beta particle was *less* effective than that from HTO or the gamma rays from ^{60}Co . The doses to the nucleus needed to produce two visible aberrations were calculated as 820 rad, 490 rad, and 520 rad for ^3H - TdR, HTO, and ^{60}Co , respectively.

Not all of the work was with cell cultures or cells extracted from treated animals. Some conventional carcinogenesis work was done in the late 1960s at the Argonne Cancer Research Hospital^(a) and Department of Radiology of the University of Chicago. Mewissen and Rust (1973), for example, reported at the Las Vegas tritium symposium on work involving over fourteen hundred newborn C57 Black/6 mice that were injected with 0.3 to 1.5 $\mu\text{Ci/g}$ body weight of tritiated thymidine with "cold" thymidine as a control. Four tumor types were studied in detail: lymphosarcoma, reticulum-cell sarcoma, hepatoma, and miscellaneous other tumors, mostly fibrosarcoma. In contrast to some of the work quoted earlier, there was a significant increase in overall tumor incidence, especially of lymphosarcoma. The total exceeded 70%, but the results indicated that the effect was more a triggering than de novo induction of the tumors.^(b)

The group at Ohio State had much interest in iodine and iodinated nucleic acid precursors. They compared intranuclear ^{131}I with ^{125}I and ^3H using a strain of leukemia cells in tissue culture. The iodine isotopes were given as iodo-deoxyuridine compounds and the tritium as ^3H -thymidine. In this work, the ^{131}I and ^3H gave almost identical results, despite their very different energies. By contrast, the ^{125}I was four to five times more toxic, and the survival curve looked like the ones typical of high-linear-energy transfer (LET) radiations such as neutrons and alpha particles. The curves for ^{131}I and ^3H were like those typical of low-LET radiations.^(c)

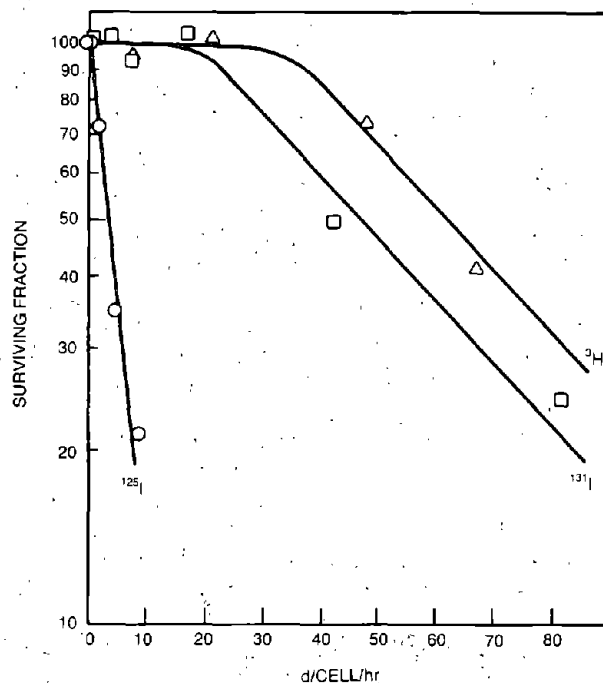
(a) Supported largely by AEC. The work also had support from IAEA, the National Institutes of Health (NIH), and Euratom in Brussels. A useful summary of the organization and work of the Argonne Cancer Hospital was supplied to the author by L. H. Lanzl. It is regretted that space has not allowed expansion upon the important contributions of this group. Many of the names have been met in earlier chapters since collaboration with ANL was close. Interested readers wishing more detail should contact the author.

(b) The policy in this book (see preface) is to concentrate primarily on reporting work done and the author's interpretation of the data, all in historical context. Critical evaluations based on subsequent work are not our primary objective, although there are some. However, it is necessary here to mention that the C57 Black mouse has such a high incidence of spontaneous tumors that complex statistical analyses are usually needed to establish an effect, and it is still more difficult to establish causation. This work should probably be repeated with one of the newer strains of mice with essentially zero incidence of many pertinent tumor types. This is especially important since there are those who believe that neither tritium nor ^{14}C is carcinogenic (Cronkite 1982).

(c) See discussion of relative biological effectiveness in chapter 10.

This contrast is shown in figure 20.4, taken from the paper by Hofer and Hughes (1971).^(a)

FIGURE 20.4. Fraction of L1210 cells surviving various radioisotope doses, plotted as a function of disintegrations per cell per hour. (Redrawn from Hofer and Hughes 1971. Reprinted with permission of Academic Press, Orlando, Florida, copyright 1971.)



This relationship shows that if there is to be anything "special" it is more likely to be resident in ^{125}I than in tritium or ^{131}I .

We have already reviewed the effects studies with tritiated water and tritium gas in chapter 10. There we concluded that, while tritium was hardly innocuous, it could be set down as a relatively benign radionuclide. Now we can say that, despite early fears of very severe damage to cells when the tritium (or other radionuclide) is placed within the cell nucleus, the effectiveness overall is not increased by so large a factor as was anticipated. Part of this is because relatively small amounts of the label actually reach the final goal. We shall examine implications of these phenomena for radiation protection in humans in section F.

E: The Transmutation Problem

In chapter 10, section IV D, we briefly mentioned the possible existence of a transmutation problem when radionuclides disintegrate within cells. We indicated that if our respective patience held out we would discuss it in connection with the toxicologic aspects of tracer chemistry and nuclear medicine. The writer's patience has held out and he hopes the reader's patience has been

(a) This is about as far into cellular radiobiology as we can go in a book devoted to the toxicology of radioactive materials. Readers interested in delving more into the derivation and usefulness of the survival curve can find a lucid explanation in the monograph by Okada already cited, and in the *Textbook of Radiation Biology* by A. P. Casarett (1968, especially chapter 7) or, if they desire to go back to the original derivations and concepts, in the classic book by D. E. Lea (1955).

similarly durable. It is a problem we cannot fail to mention, even though it has turned out to be largely a "red herring" for practical radiation toxicology. If we did not discuss it, someone would dredge it up *de novo*.

The "Transmutation Problem" refers, of course, to the fact that in many radioisotope decays the product is a different element from the original.^(a) Theoretically, a possible transmutation effect might be resident in every situation we have discussed. However, relatively few of the radionuclides we have dealt with become incorporated in biologically critical molecules, and hence the transmutation to a new element is a trivial matter. Furthermore, even at high concentrations of radionuclides, the number of atoms undergoing transformation is a tiny fraction of the atoms in cells and tissues. However, there is not so much redundancy in the cell nucleus or in critical molecules such as DNA or RNA. Also, the elements of primary interest, phosphorus, tritium, carbon, and iodine are easily incorporated into the basic structure of the nucleic acids, and it is conceivable that transformation of phosphorus to sulfur, tritium to helium, or carbon to nitrogen, for example, in the backbone of the cell's growth and hereditary mechanism might be damaging in a special way. This includes sometimes a transfer of electrical charge.

The only way to attack this problem experimentally is to do careful dose-response work and see if the effects can be accounted for on the basis of the radiation dose, or if they markedly exceed those expected from the calculated dose. (It would have to be a fairly substantial effect because of the inaccuracies of the dose calculation.) All of the work has involved cellular-level systems.

Radiophosphorus. Early work concerned the transformation of phosphorus to sulfur. The ^{32}P beta particle is of such high energy that even when incorporated into DNA much of the energy is dissipated outside of the nucleus. Hershey et al. (1951) at Washington University in St. Louis and Stent and Fuerst (1955) at Berkeley showed clearly that lethality in bacteriophages resulted from transmutation when ^{32}P was incorporated. Also, it appeared, as we saw in table 20.2, that every decay produced a break in the single-stranded DNA of such a simple system. As reviewed by Krisch and Zelle (1969)^(b) and in the NCRP report already cited (NCRP 1979), evidence of a small transmutation effect in *Drosophila* also appeared. In mammalian systems, it was clear that the process had a very low efficiency.

Tritium. Much more work has been done with tritium than any other incorporated radionuclide, largely because the transformation from hydrogen to

(a) Sometimes the term includes all of the phenomena except the release of ionizing radiation. In addition to chemical change due to the atomic number change, there is the possibility of production of an excited chemical state, nuclear recoil effects, etc., all at a very local level. There is no strict tradition in radiation biophysics as to which definition to use for transmutation, the total of the local effects or only the effects of chemical change due to change in atomic number. For the weak beta emitters of primary interest to us here, recoil and excitation effects are expected to be very minor, with the possible exception of ^{32}P . An excellent discussion appropriate for the biomedical scientist of the local effects and those along the path of the beta particle is given in the review of transmutation effects by Krisch and Zelle (1969), written while Zelle was Director of the Biology Division at ANL.

(b) This review is among the most complete and readable descriptions of the phenomena and experimental work to the date of its writing.

helium would almost certainly break the important carbon-hydrogen bond, thus changing the molecule chemically. It can also result in a positively charged carbonium ion. Much of the interest began and has persisted at Brookhaven, at Berkeley, and at Penn State.

A review of experiments with mammalian cells by Bond and Feinendegen (1966) led to the conclusion that somatic effects could all be accounted for by calculated average radiation dose down to 5 rad or less; this means down to a mass of 10^{-11} g or less. They further concluded that the tritium atoms are randomly distributed into the DNA and that every part of the cell lies within range of at least one tritium beta particle. The work was reevaluated by Feinendegen and Bond (1973). While the story for mammalian cells held up, some exceptions had begun to appear. These were further evaluated by Carsten (1979) as part of his important sequence of investigations on environmental tritium (chapters 10 and 13).

A transmutation effect from incorporated tritium was demonstrated in microorganisms such as the bacterium, *E. coli*. Varying the position of the tritium atom in the protein precursors was the key. In general, all effects could be accounted for entirely on the basis of the beta-particle dose, with the exception of three cases involving mutagenesis. When the tritium was given in uridine or uracil^(a) rather than thymidine and placed in the number 5 carbon of the ring, it was seven times as effective in producing mutations as decays from tritium in the number 6 ring carbon. A mechanism was suggested by Person, Snipes, and Krasin (1976) working at Penn State. They also showed that tritium located in the 6 position of the thymidine ring or the 2 position of the purine, adenine, produced significantly more effect than in other positions or expected from the beta dose. Thus, under special circumstances, a real transmutation effect can be demonstrated in bacterial systems.^(b)

Work with the fruit fly, *Drosophila*, done at Leiden in the Netherlands by Kieft (1968) indicated a somewhat similar situation. Again the 5 position in uridine appeared to be the most effective. The extra effectiveness was a factor of two to three rather than the factor of seven seen in *E. coli*. Again also the phenomenon was limited to mutations, or appeared to be. Some work on carcinogenesis in *Drosophila* by Ghelelovitch (1969) indicated a reverse situation with tritium in the 6 position being more effective. Unfortunately, the *Drosophila* work did not have the benefit of measurements of tritium incorporation in the cells and tissues, and we thus have no dosage calculations. The evidence is limited to the similarity of the position effect to that seen in bacteria.

Meanwhile, work with mammalian cells continued to show no measurable transmutation effect. Lambert, at the Radiological Protection Service in the United Kingdom, measured cytological damage in mouse testes. He could find no difference between either x rays delivered at an exponentially decreasing dose rate to imitate the kinetics of a dose from tritium (compare chapters 8 and 10)

(a) Uridine, uracil: nucleic acid or protein precursors.

(b) This conclusion is not accepted for lethality or other processes, only for mutations. Even for them there are those who postulate that the special effectiveness could as well be a "more efficient irradiation" of the DNA by a positional effect in the molecule. Such positional effects have been shown in inactivation of bacteriophage (Feinendegen and Bond 1973).

and beta doses delivered from either tritiated thymidine or tritiated water in producing cell death over a seventy-two-hour period (Lambert 1969).^(a)

Cleaver, Thomas, and Burki (1972), at the University of California, San Francisco and Berkeley, did a suicide-type experiment with Chinese hamster cells and measured DNA strand breaks. Although the dose-effect curves had different slopes, they concluded that the damage resulting in this system from decays of ^3H -TdR in DNA is no greater than that predicted from the beta-particle irradiation.

Each of the studies cites work of others with similar outcomes. Feinendegen and Bond (1973) completed their re-examination of the old evidence and the new evidence to 1973 with the conclusion that no modification of the earlier statements was needed, i.e., that transmutation is not a significant factor in the effectiveness of tritium decaying in the nucleus of mammalian cells. No one since has found reason to modify this view. However, it is also generally accepted that certain bacterial cells (perhaps all prokaryotic cells)^(b) and mutations in *Drosophila* are different from mammalian cells mechanistically.

Other Radionuclide Labels. What can be said about transmutation by the other low-energy, short-range radionuclides that, like tritium and phosphorus, can be incorporated into the biologically important precursors of cell growth and division? The best sources of information on these are NCRP Report 63 (NCRP 1979), especially Section 3.4 and Appendix VII and, the review by Kršich and Zelle (1969).

When ^{14}C decays, the result is a nitrogen atom, a situation that can break important molecular bonds and possibly contribute to cell damage. Such work with ^{14}C is very difficult. Because of its long half-life, undesirably high specific activities are needed. Also, its energy, while low by most standards, is high enough that a larger proportion of its deposition may be outside of the labeled nucleus. Nevertheless, some information on chromosomal aberrations and mutations suggests a transmutation effect in material such as onion root tips and bean plants and *E. coli* and possibly in *Drosophila*. Again, it is only when the label is in a specific position, this time the 2 position in thymidine, that the effect is noted. However, there have also been many completely negative experiments. On balance, the effect would appear to be negligible. If any extra effectiveness applies only to one position, labeling of that position would normally be quite infrequent and the effect thus lost in the "noise" of other events.

Sulfur-35 decays to ^{35}Cl , and this might produce transmutations if there were much sulfur label in the nucleic acids. However, it appears that ^{35}S does not get incorporated into DNA. It is not surprising, therefore, that work at Reed College by Hungate and Mannell (1952) using the fungus *Neurospora* was negative.

(a) The initial results indicated that the ^3H -TdR was about four times as effective as HTO on the basis of injected dose. However, dose calculations showed that the 20 μCi of HTO gave a dose of 12.2 rad to the testes and therefore to the cell nucleus, and the 5 μCi of ^3H -TdR/g body weight delivered about 14.7 rad to the nucleus. The external dose from the x rays, for equivalent effect, was about 30 rad. Lambert considered the problems of dosimetry sufficiently complex to regard these results as in essential agreement, although he did suggest an RBE for tritium greater than unity as we saw earlier.

(b) Cells with their nuclear material scattered in the cytoplasm rather than gathered in an organized nucleus.

The story with iodine isotopes is essentially negative, despite many attempts to find transmutations from the widely used iodinated compounds. Only in the special case of ^{125}I with its Auger electron effect is there a special effectiveness. And this is not a transmutation effect at all. (a)

It should be stressed here that, even though there does not appear to be a transmutation effect of significance for mammals, the work was eminently worth supporting. First, we would still have the nagging worry over a possible transmutation effect in potential exposures of humans unless the host of workers (only some of whom we have cited) made these careful studies. Second, the development of ideas about mechanisms of mutation was materially advanced and so was cellular biology by the application of this unique extension of radioisotope toxicology. The support of government for such work has been of the greatest importance.

F. Implications For Man

It is customary among those working in nuclear medicine and tracer chemistry to state that exposure of man to the labeled precursors of cell growth and division that we have been discussing in this section is trivial. In comparison to the millions of exposures to other compounds occurring in nuclear medicine, this is indeed true. Also, the handling of the tritiated, iodinated, and other labeled moieties in tracer chemistry is usually done in large institutions with well-organized radiation protection services. Nevertheless, the subject of possible exposure of humans cannot be, nor has it been, dismissed. Let us review the evidence gathered in part.

We can relax about transmutation. Only under very highly specialized laboratory conditions requiring special efforts to incorporate the radionuclide into a specific position in a specific molecule can this effect be important. Even this seems not to apply to mammalian cells. For ordinary environmental or laboratory exposure, a very small percentage of incorporations go into the specific molecule of interest and only a small percentage of these go to the critical position. Only after long-term chronic exposure would there be measurable incorporation in vivo.

What of planned administrations to patients? The importance of the labeled compounds as tracers for the development of cell lineages and for determination of cell growth rates and mechanisms inevitably led to a few instances where the animal data simply would not suffice. The process had to be studied in humans to depict their unique cell production and lineage processes. Tracer-level doses have been given to selected patients. Examples are:

1. Labeling indices of normal and malignant cell populations that have occasionally been studied in vivo, largely by the Brookhaven group. See, for

(a) The Auger effect is described well for biomedical scientists by Krisch and Zelle (1969). Electron capture is the first event, which results in a vacancy in the inner shell of the atom, which is filled by an electron from the outer shell. Considerable energy is released locally in this process, and it may cause the ejection of another electron with a repetition of the whole process. Thus, the effect described by Auger has been called a vacancy cascade. It can produce intense but very localized energy releases. Rosalyn Yalow refers to the vacancy cascade as "catastrophic" decay (as mentioned by Myers 1984).

example, Cronkite et al. (1962), especially table IV, p. 201 and citations therein. Incidentally, the labeling index was lower than for rapidly growing cells of the blood-forming system.

2. Work by the Brookhaven group with a brain tumor patient who was terminal and comatose (Johnson et al. 1960). Injections of ^3H -TdR were given at times calculated to be close to the end of the patient's life, and the labeling of the neoplastic cells in the brain tumor was studied post-mortem by autoradiography. It appeared here, also, that the cancer cells were dividing more slowly than nonneoplastic cell populations.
3. A series of studies by Martin Lipkin and associates at Cornell University Medical College and Sloan-Kettering Institute for Cancer Research in New York utilized tritiated thymidine to measure generation times and phases of the proliferation cycle in cells of the human intestinal tract. This was very complete work. A pair of papers in 1963 described work on patients requiring surgery of the colon and rectum (Lipkin, Bell, and Sherlock 1963) and of stomach and ilium in addition (Lipkin, Sherlock, and Bell 1963). The doses of tritiated thymidine were very low (0.02 to 0.26 $\mu\text{Ci/g}$) and would thus be of no significance from a radiation protection standpoint. Most of the later work utilized animals or in-vivo techniques, but Lipkin has established the cell sequences and turnover times throughout the human gastrointestinal tract. All of this was by use of tritiated nucleic acid precursors.
4. In addition, work was done at Western Reserve University on the cell renewal processes in human rectal mucosa (Cole and McKalen 1961, 1963), which further documents uses of these labeled compounds in man. Here 10 mCi of tritiated thymidine were given to patients shortly before surgical removal of a section of the colon. In one case, biopsy material was obtained at 27 to 291 hr after surgery and the rates of cell renewal measured. In another, the growth of adenomas was measured. Somewhat similar work was done in laboratories outside of the United States.

Obviously, these are not the only such studies. There have been many others, although it must be said that most of them were concentrated in the era of the late 1950s and early 1960s. It is obvious that such procedures have been rare. Most of the labeling of human cells has been done in vitro.

Other areas of planned administrations that might involve nuclear labeling or at least specific irradiation of growing cells occurred in attempts at therapy, e.g., the use of ^{32}P in the early days of possible leukemia therapy; also the ubiquitous iodine compounds, and the occasional special compound such as a tritium-labeled drug tried for the treatment of cancer (Marrian et al. 1962).

The uses of these compounds in tracer chemistry cannot be dismissed as of no potential hazard to humans. While the chances for ingestion or inhalation are small in comparison to releases of these same radionuclides from nuclear installations or weapons, the total amounts used in major research institutions are very large. Nearly every major biomedical research installation uses from one to many of these substances. There are opportunities for release during synthetic chemistry and waste disposal procedures. Most radiation safety officers worry about their control and try to keep a close rein on their handling (Baily 1982).

That implications for humans are worthy of careful thought is amply confirmed by the fact that the NCRP convened the committee that wrote Report No. 63 (NCRP 1979) not only to review the science but to make

recommendations regarding permissible exposure levels. The Council found it necessary and advisable in some cases to recommend figures that differ from "normal" intakes of the same radionuclides. For example, a single intravenous injection of tritiated thymidine was considered about 4.3 times as effective as tritiated water and a single ingestion dose 8.6 times more effective than tritiated water. For continuous intake, a further factor was added. The same limits were suggested for other tritiated precursors, even though they incorporated less efficiently than thymidine. This is because of evidence that some of the substances are radiosensitizers. The report also suggested that the same limits be applied to RNA precursors as to tritiated thymidine.

By contrast, tritium-labeled amino acids and nonspecific precursors are not considered different, and the usual criteria for calculating dose in *tissue* rather than in cells should apply to these in the opinion of the NCRP committee.

For ^{14}C labeled compounds, the calculations showed that a bit of relaxation of allowable amounts would be in order, viz., 1.47 times as much ^{14}C -thymidine could be allowed as ^3H -thymidine, with an upper limit of 2 mCi to adult man. There was a tightening of restrictions for ^{14}C RNA precursors compared to ^3H RNA precursors, by a factor of eight in intake.

With ^{32}P and ^{35}S , it was concluded that no special consideration need be given to decays in the cell nucleus because of the relatively high energy and long range of the beta particles from these elements. Here, the ordinary concept and calculation using average dose to the organ was considered to apply.

With iodine, the precursor is 5 - iodo - 2 - deoxyuridine (IUdR), which is incorporated into DNA much as is thymidine. This iodine is labile, however, and soon enters the inorganic pool. Thus, for all isotopes but ^{125}I , the ordinary procedures are recommended. Through a series of calculations involving the Auger effects, or comparable processes (which showed a factor of twenty-five-fold higher toxicity for ^{125}I compared to ^3H and an efficiency of incorporation of $^{125}\text{IUdR}$ versus ^3H thymidine of one sixth) it is concluded that intakes of $^{125}\text{IUdR}$ should be about one-quarter those of ^3H -thymidine. (The actual intake limits vary with the route of entry, of course.)

The new ICRP publication on radioisotope standards for occupational exposure (ICRP 1979, 1982) sets aside a special category only for organic compounds containing ^3H and ^{14}C . Otherwise the broad limits on annual intake do not specify the nature of the compound, and by implication negate there being a need for separate consideration of situations when the cell nucleus is irradiated specifically. Perhaps these will be added when the ICRP addresses population exposures.

From the NCRP work, we see that the compounds of tritium, ^{14}C , and ^{125}I require special restrictions. Since these are among the most likely to be encountered, the restriction is of some practical importance.^(a) We should remember, however, that these restrictions are applied to radionuclides that have some of the highest permissible intake levels extant. Furthermore, the factor between organic compounds within cell nuclei and ordinary compounds is seen to be considerably less than the factor of one hundred that led Allan Brodsky to his great enthusiasm for tritium (see p. 1742). In the overall picture of radioisotope

(a) The people of the U.K. Radiological Protection Service made it even more practical by going to recommended maximum annual intakes for a variety of compounds of tritium and ^{14}C . The values for ^{14}C -labeled compounds are in general lower (Vennart 1969).

toxicology, these special substances are still relatively innocuous in comparison, let us say, to plutonium. Yet, they have potentials that mean that vigilance must be maintained.

These conclusions were gained only after large amounts of hard work in a number of laboratories and bespeak again the importance of support for the work.

IV. Specifics

In this section, we will take up some areas of work that have different implications from either dosimetry or cellular-level effects, which were reviewed in sections II and III. They are mostly specific to our intention of considering work related primarily to the radioisotope toxicology programs that have been the focus of interest in this book. Much has obvious toxicologic overtones. Some is taken up primarily because it represents work done in the same laboratories and by some of the same people supported by the radioisotope toxicology venture. Obviously, there is no intention of entering a comprehensive review of either tracer chemistry or nuclear medicine. Ample reference has already been made to reviews of these.

The work we will consider falls rather easily into distinct periods. The first concerns the resurgence of activity that began at the end of World War II and developments over the next decade and a half. It was a mixture of developing diagnostic and therapeutic uses of radionuclides. Because the initial emphasis was on therapy, I am calling this first period "The Era of Therapeutic Intent." It runs from about 1948 to about 1965. The second era, which began in roughly the mid 1960s and continues today, has concentrated on improvements in diagnostic procedures and is being called "The Era of Ever More Scanning and Ever Shorter Half-Life Radionuclides." A third era with a resurgence of therapeutic intent may develop out of very recent work.

Toxicologic and mechanistic considerations had important influences on each era, but they were quite different.

A. The Earlier Years—The Era of Therapeutic Intent

We have already mentioned that uses of radionuclides for therapy of disease states played a prominent role in the thinking of the pioneers in what was to become nuclear medicine. We have also seen a few examples. In the succeeding sections we will review some others.

1. Atoms for Peace

Officially the "Atoms for Peace" program was launched during the Eisenhower administration (good years for American science)^(a) with the first of the two

(a) This remark should not be interpreted to mean we know they would have been any different had Adlai Stevenson been in the White House. Conditions were very favorable for major advances in scientific research of all kinds.

Atoms for Peace conferences held in Geneva, Switzerland, in 1955.^(a) At these, the international community took the wraps off its developments in nuclear energy. However, in terms of availability of radionuclides for medical uses and for research in the United States, the bonanza had already started. Indeed, the Oak Ridge reactor (Clinton Laboratories at the time) had more radioisotopes than it knew what to do with, even before the end of World War II. Many were separated, purified, and sent to Berkeley, from which they were distributed. They were made part of the program of distribution of accelerator-produced isotopes that Berkeley already had under way. The recipients were not aware that in some instances they were receiving radioisotopes produced in a nuclear reactor. It was not yet time to break security and announce the real source.

Overt distribution of reactor-produced isotopes outside the Manhattan Project began on August 2, 1946. In January 1947, direction of the program was transferred to the newly formed AEC. Dr. Paul Aebersold, originally at Berkeley, but later at the Oak Ridge reactor, was put in charge of the Isotopes Branch of the AEC and did a superb job of meeting the needs of both science and medical practice. During the first year, over eleven hundred shipments of reactor-produced radioisotopes were made to 160 organizations and institutions. Aebersold tells the story in a paper (Aebersold 1948) given at one of the first postwar symposia held on the use of isotopes in biology and medicine. An excerpt from the conclusion of Aebersold's paper not only gives more detail but a feel for the enthusiasm for the program felt by all concerned.

The present situation respecting the availability of isotopes is indeed a happy one. Almost every useful isotope which is found in nature or producible by man is now available for the investigator, and the few that are not yet generally available can be expected to become so. Advances in biology and medicine through the use of isotopes will henceforth be limited only by the availability of personnel and facilities and by the imagination of the investigators.

This favorable situation has been the result of the interest, effort, and cooperation of a number of organizations and hundreds of persons both within and outside the Commission's program. Many sacrifices have been made in individual programs to promote the availability of isotopes. It would be impossible here to give due credit to all those who have contributed. Recognition for radioisotope distribution must be given particularly to the cooperative activities of the Chemical, Technical, and Production Divisions, and the Health-Physics Department and management of the Clinton Laboratories, which is operated for the government by the Monsanto Chemical Company.

(a) Admiral Lewis L. Strauss was chairman of the AEC at this time. He had President Eisenhower's ear, and while it is difficult to trace details, it appears likely that Strauss helped to include some of the biomedical facets of the program. Admiral Strauss's autobiography contains a moving section describing Eisenhower's speech to the United Nations on the Atoms for Peace program and the ovation it generated (Strauss 1962). His first sentences from the chapter entitled "The Peaceable Atom. . ." are worthy of note in their own right, "Providence has a way of redeeming man from his follies and even from his sins. Since time immemorial, man's inventiveness has been stimulated to produce weapons and engines for use against his enemies, most of which were eventually turned upon the inventors themselves. But finally these devices often were transmuted into peaceful tools." (Strauss 1962, p. 330)

Groups in other Commission laboratories, notably the Argonne National Laboratory and the Radiation Laboratory of the University of California, have made valuable contributions to basic radiochemical and physical techniques.

Distribution of deuterium, both gas and oxide, is being handled ably by the Stuart Oxygen Company of San Francisco. The deuterium oxide was produced by other facilities under the Manhattan Project program.

It is appropriate to add here that the Atomic Energy Commission is keenly aware how important the proper availability and distribution of isotopes is to scientific, technical, and medical progress. So far as is compatible with the Atomic Energy Act, which gives it a virtual monopoly of the distribution of many isotopes and charges it with maintaining certain controls, the Commission will promote a program that will be of increasing benefit to scientific advance and human welfare.

In closing I should like to add that the Commission is naturally much interested in the dissemination of information and in training which will advance the proper use of isotopes. This is indicated by the official participation here of many persons from Commission laboratories and by the routine declassification of information related to isotope applications.

It is well to recognize, however, that (1) other important Commission activities are in serious competition for Commission personnel and facilities; (2) the Commission's informational and training activities operate under limitations to which educational institutions are not subject; and (3) much more research with distributed isotopes is done outside Commission laboratories than inside them. Thus educational institutions are in a position to take the lead in promoting education and training in isotope applications. The University of Wisconsin is to be congratulated on the timely and valuable contribution in that direction made by this excellent Symposium. (Aebersold 1948)

A later paper by Aebersold (1956) gives considerable perspective for the uses of the radioisotopes produced. It was an era of almost missionary zeal.

Note that the program included stable as well as radioactive isotopes and involved facilities other than the Clinton Laboratories reactor. Prices paid were nominal in most cases. By August 1, 1966, there had been over two hundred thousand shipments of radioisotopes involving over 5.5 million *curies* of radioactivity. Another 2.5 million *curies* went out from other AEC installations (Brookhaven, Mound Laboratory, the Savannah River Project, and Idaho operations).^(a) The obvious crescendo was associated with the official "Atoms for Peace" program and included a large number of individual physicians and researchers who had been trained and met the licensing requirements of the AEC. Much of the training was provided by AEC through intensive short courses at Oak Ridge, summer institutes at many laboratories, and formal degree programs at universities.

The cyclotrons did not shut down during this period. Many isotopes can be prepared satisfactorily only with the cyclotron; others are best prepared in the nuclear reactor. However, it was the availability of large quantities from the reactor that took the lid off the development of therapeutic applications.

(a) Some of this information is from a manuscript for a speech given about 1967 by C. L. Dunham, M.D., Director of the Division of Biology and Medicine, AEC, and kindly supplied to me by Dr. H. D. Bruner, one of Dunham's colleagues, who may well have helped write the speech.

2. Radioiodine

We saw in chapter 5 the development of radioiodine uses by the Berkeley and the MIT-MGH groups in the prewar years (Hertz, Roberts, and Evans 1938).^(a) Its remarkable affinity for the thyroid gland has not been equaled by any other isotope toward any organ. As soon as sufficient quantities were available, it was pressed into service for therapy of thyroid disorders. Pioneered by the Berkeley and MIT-MGH groups, even before large quantities were available, iodine, principally ^{131}I , has taken its place beside surgery in cases of chronic overactivity of the thyroid gland (thyrotoxicosis, Graves' disease).

Perhaps the easiest way to see what was done with iodine before World War II is to consult chapter 5 herein and Marshall Brucer's essay, "Genesis of Thyroid-Radioiodine . . ." done as part of the series of *Vignettes of Nuclear Medicine* (Brucer 1978). For the status immediately postwar, the collection of papers from the first postwar iodine symposium directed largely toward clinical uses held at the then-new Brookhaven National Laboratory (BNL) in July 1948 (BNL 1948) gives reviews done in an informal atmosphere.^(b) This latter volume includes, particularly in the paper by R. W. Rawson (Memorial Hospital, New York), a cogent review of the "firsts" in this field.

Iodine in large doses is especially useful in cases where risk of surgery is great, for example in cases of chronic heart difficulties associated with the overactive thyroid. The cure rates have been impressive. Nevertheless, it is our duty, as it was of the attending physicians, to consider any untoward toxic sequelae. This work was begun in MED and AEC installations, and there is an ample literature. We will consider some highlights.

Immediate side effects can be related to local irradiation of surrounding tissues. Sometimes there is temporary exacerbation of the hyperthyroidism, especially after large doses of ^{131}I . A more important, indeed the chief undesired effect following iodine treatment is the development of underactivity of the thyroid (hypothyroidism). This is not surprising when one realizes that the doses used generally cause complete ablation of the gland. The occurrence of

(a) While there is no question that the original animal work was done by the MIT-MGH group, and the first uses of iodine in human diagnosis occurred at Berkeley and at MIT-MGH, it is possible that therapeutic uses of ^{131}I began independently in other places as well. For example, Dr. William F. Bale recalled in personal interview (Bale 1979) the case of a small boy at Rochester with thyroid cancer. The surgeons had removed as much tissue as possible, but there was still a tumor underneath where they could not work. They thought of ^{131}I treatment, but the University of Rochester's cyclotron as then constituted could not make enough of the isotope. Dr. Bale was going to St. Louis for a scientific meeting (about 1945) and persuaded people at Washington University's cyclotron (Professor Hughes) to run the machine all the time he was there to make enough radiotellurium for the purpose. It went back to Rochester in the baggage car on the same train as Dr. Bale. Immediately on arrival, they taught themselves some "hot tellurium" chemistry and had radioiodine on a scale never seen before at Rochester. The boy received several millicuries of ^{131}I and the tumor regressed. He later received a dose of ^{131}I via the Oak Ridge program. Fifteen years later (approximately) he was back to see Dr. Bale and was apparently in good health. This episode is described partly to indicate how the ideas spread or even arose de novo in different places, but primarily to show the lengths many nonmedical people went to in fostering what is now called nuclear medicine.

(b) And the price for the proceedings was listed as forty-five cents!

hypothyroidism is about 20% in the first year and rises gradually to about 50% at fifteen years (Chapman 1965). The same effect appears after surgical ablation, but the higher doses of ^{131}I appear more prone to produce hypothyroidism. This is illustrated in figure 20.5, taken from a definitive review by Maxon et al. (1977) working at Cincinnati.^(a) This induced hypothyroidism is not a serious problem so long as replacement therapy remains effective and easily available.

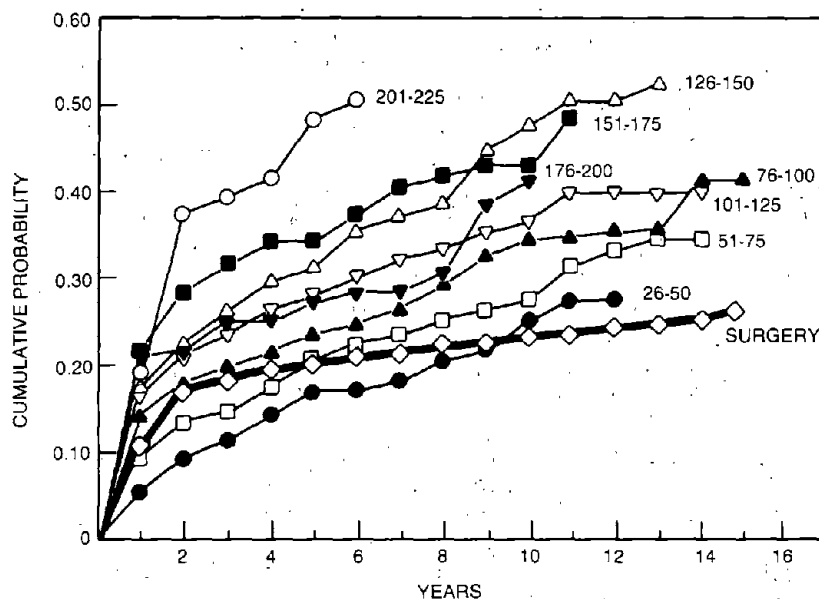


FIGURE 20.5. Probability of becoming hypothyroid with a single treatment of ^{131}I for Graves' disease. The numbers on the curves show the ^{131}I dose in microcuries per gram of thyroid. From the Cooperative Thyrotoxicosis Follow-up Study. (Redrawn from Maxon et al. 1977. Reprinted with permission of the American Journal of Medicine, New York, copyright 1977.)

There was, of course, ample experimental work with animals to precede or extend to higher doses all of the experience with patients. Special mention should be made of prewar work at Berkeley (remembering that the original work of Hertz, Roberts, and Evans was done with rabbits at MIT-MGH in 1938), Hamilton, Soley, and Eichorn (1940); Hamilton and Soley (1940); and the post-war work of Durbin et al. (1958a) on the long-term sequelae of massive doses of ^{131}I in rats; and of Watts and Durbin (1956) on distribution and acute effects. It was quite clear that the high levels (10 to 90 $\mu\text{Ci/g}$) retarded growth and destroyed the thyroid. There was, in addition, chronic renal damage, atrophy of the spleen, lymph nodes, and thymus and earlier appearance of mammary tumors, although the incidence was not related to ^{131}I dosage. In later work, Durbin

(a) The Cincinnati General Hospital and the University of Cincinnati have been a major center for thyroid work for many years under the capable leadership of Eugene Saenger.

et al. (1961) concluded that these and other sequelae involving the anterior pituitary gland and adrenal were consequences of *both* radiation damage and deep and prolonged endocrine deficiency. Thus, we see that the toxicologic enterprise had been doing its bit. There was much more.

Particular concern developed around the possible increased occurrence of leukemia in patients who had had thyroid ablation with radioiodine. It was already known that thyrotoxicosis patients had an increased risk of leukemia. Would the radiation treatment amplify this tendency?

This concern led the Bureau of Radiological Health of the U.S. PHS to set up a formal retrospective epidemiologic study called "The Cooperative Thyrotoxicosis Therapy Follow-up Study." Over thirty-six thousand treated patients and suitable controls were included. There were twenty-five medical institutions in the United States and one in England that provided data. The results are nicely summarized by E. Tomkins (1970) and by Saenger, Thoma, and Tompkins (1968). The incidence rate of leukemia, age-adjusted, was eleven per one hundred thousand patient years in the ^{131}I -treated patients and fourteen per one hundred thousand patient years in those treated by thyroidectomy. While this does not necessarily mean that surgical ablation is *more* likely to result in leukemia, the evidence clearly does not implicate the radioiodine treatment.

The same general conclusion, although somewhat more guarded, was drawn from a study in the United Kingdom done earlier (Pochin 1960).

A much more difficult situation surrounded the plans for therapeutic uses of radioiodine for the treatment of thyroid cancer. Early work in a number of laboratories showed, using tracer-level administrations, that the uptake of iodine by tumors of the thyroid was quite unpredictable. Some tumor types took up iodine almost as avidly as normal thyroid tissue. Others took up almost no radioiodine. The same held for metastases of the various tumor types. A pattern was gradually worked out so that radioiodine therapy could be applied to those tumor types that would take up iodine. In such cases, the nodules regressed, the bone pain that often accompanies thyroid cancer disappeared, and the indication of lesions on the scan also disappeared. Thus, the results can be positive, and the effort has its place, frequently as an adjunct to surgery. However, there is not the universal effectiveness seen in the treatment of toxic goiter.

Much effort has been expended to find out why some tumors take up iodine and others do not; also to change recalcitrant ones into receptive ones. The effort has given some leads but no final solutions.

The other side of the coin is whether or not radioiodine treatment can induce cancer in glands treated for other purposes. We looked at the low doses associated with fallout or routine releases from nuclear energy installations in earlier chapters. The doses used in therapy are, of course, much higher. There is a small but finite risk involved, higher in children than in adults, as shown by a number of surveys that we do not have space to elaborate upon. The appendix on iodine of the AEC-Reactor Safety Study (Reactor Safety Study 1975) done partly by Maxon at Cincinnati, the review by Maxon et al. (1977), the review by UNSCEAR (1977), and a Swedish study (Holm et al. 1980) all point in the same direction, but only the bold will decide whether or not risks of the order found are "acceptable." The chief problem is those persons irradiated at an early age who have many decades ahead in which effects could be manifested. Also, the long-term view may be more problematical for those receiving moderate doses that do not ablate the gland than for those receiving doses that caused

ablation. A very conservative view (Emerson and Braverman 1980) in a very conservative journal suggests it may take several generations to investigate the more subtle long-term impacts.

An overview of risks derived tentatively by Maxon et al. (1977) gives us a status report, even though the absolute values of the numbers are not settled. They are shown in table 20.4, which is taken from the Maxon paper.^(a)

TABLE 20.4. Absolute Risk* of Thyroid Abnormalities After Exposure to Ionizing Radiation

Type of Abnormality and Population Surveyed	Mean Dose or Dose Range (rem) for Which Data Were Available	Absolute Risk*	Statistical Risk Range†
— Internal Irradiation (¹³¹ I) —			
Thyroid nodularity			
Children	9,000	0.23	0 to 0.52
Adults	8,755	0.11	0.06 to 0.15
Thyroid cancer			
Children	9,000	0.06	0 to 0.16
Adults	8,755	0.05	0.038 to 0.066
Hypothyroidism			
"Low dose"—children	<10 to 1,900	4.9‡	3.9 to 22.9
"High dose"—adults	2,500 to 20,000	4.4	2.8 to 7.6§
— External Irradiation —			
Thyroid nodularity in children	0 to 1,500	12.3	4 to 45
Thyroid cancer in children	0 to 1,500	4.2	0.9 to 17.3
Hypothyroidism in adults	1,640	10.2	0 to 25

*In number of cases per million persons per rem per year.

†Unless otherwise indicated, the risk range was determined by using the assumption that the number of cases, n , out of the population at risk represents the true mean of a Poisson distribution. The range is then estimated by using $n \pm 2\sqrt{n}$ in the calculations to establish the 95 per cent confidence level.

‡Threshold of 20 rem.

§The value of 4.4 is taken from the mid-point of the dose range in question.

||In these cases, the risk was determined from the slope of the linear regression line. The range was estimated from the extreme data points, which provide the lowest and highest slopes.

Source: Reset From Maxon et al. 1977. Reprinted with permission of the American Journal of Medicine, New York, copyright 1977.

Several important points can be derived from this summary table:

1. The difference between children and adults is marked for the development of thyroid nodularity but not so large for thyroid cancer induction.

(a) The substance of this paper and other aspects are contained in a recent NCRP Report (NCRP 1985c) produced by the task group of which Dr. Maxon was chairman.

2. The risks of developing hypothyroidism appear higher than the risks of either nodules or cancer.
3. External radiation (x rays) is, in general, more risky than radioiodine (^{131}I).

This last point has been noted in animal work also (e.g., USSR work quoted by Maxon) and seemed to be about to become a maxim. Indeed, possible explanations, most of them referable to a dose-rate effect, have been suggested. Very recently, a comparison of ^{131}I and *localized* irradiation of the thyroid and pituitary glands of Long-Evans rats (Lee et al. 1982) has found no differences in effectiveness. Only still further work can settle the matter. There is much evidence for an extra effectiveness of external sources^(a) and there are some problems with the study by Lee et al.

The chances for some sort of untoward effect of large doses of radiation to the thyroid are certainly not negligible. The benefits of the treatment may more than compensate for the risk, but judgments need to be made quite regularly and carefully.

On the diagnostic side, where iodine is used either as the inorganic ion or incorporated in special compounds (e.g., iodinated rose bengal), the doses are very low and getting lower each year. While the linear no-threshold extrapolation (chapter 16) predicts a finite risk at any dose, the chances of significant long-term effects *in a given individual* are likely to be unmeasurable. Only by considering large populations can the probabilities of toxic effects be approached.

A picture that any book concerning the history of radioisotopes would be incomplete without is shown in figure 20.6. This shows a little girl at Berkeley having her thyroid radioiodine content counted with one of the old clumsy Geiger-Müller counters. It was published in 1942 by Joe Hamilton.



FIGURE 20.6. Early arrangements for counting activity of radioiodine in the thyroid gland, about 1941. (From the files of Dr. J. Hamilton, courtesy of Dr. P. W. Durbin, Lawrence Berkeley Laboratory.)

3. Astatine

The story of astatine took place entirely in one laboratory, the University of California at Berkeley. Astatine was isolated in 1940 by transmutation of bismuth by alpha particles at 32 MeV in the 60-in. cyclotron at the Crocker Laboratory (see chapters 6, 7, and 8). It had properties of the halogen group, and its chemical, physical, and nuclear properties established it as element 85. It was first called "Eka-Iodine." The name astatine was derived from the Greek word for

(a) This extra effectiveness is reiterated in the cited NCRP Report (NCRP 1985b), but it is lowered to a factor of only three.

"unstable." It emits alpha particles, the only synthetic radioelement to do so up to that time, of about 6.9-MeV average energy and an 80-keV x ray, handy for in-vivo counting, with a half-life of only 7.3 hr.^(a)

As soon as possible, Hamilton and his group investigated its metabolism in guinea pigs and found that it behaved as a halogen should. It was taken up with considerable avidity by the thyroid gland (Hamilton and Soley 1940). The uptake was less than half that of iodine, but still enough to suggest possible usefulness in therapy. This was particularly intriguing because of the high effectiveness, known qualitatively even then, of the alpha particle. Also, its excretion rate, greater accumulation in hyperplastic (i.e., "thyrotoxic") thyroid glands, and other properties stimulated its active consideration as a substitute for radioiodine in therapeutic applications. This led to a flurry of activity with animals at the Crocker Laboratory as a prelude to human trials.

A summary was produced in 1953 as one of the University of California Publications in Pharmacology series (Hamilton et al. 1953). There is extensive autoradiographic information, along with biochemical determinations and detailed studies of effects in rats and monkeys. The metabolism of ^{211}At and ^{131}I resemble each other, primarily in their considerable deposition in the thyroid gland. In almost all other tissues, there was more astatine than iodine. This indicated that the "figure of merit" for astatine would be much lower than for radioiodine. Nor was the concentration in thyroid as high relatively as that of ^{131}I . Thus, the possibility of radiation damage to other tissues appeared greater. Nevertheless, the localization was still highly selective and promising.

The effects work showed that astatine could produce profound effects in the thyroid gland with no injury to the immediately surrounding tissues, including the parathyroid gland, an advantage over iodine. There were easily measurable effects on the body weight, white cell counts, etc., which recovered fairly completely.

In 1954, there was a series of reports from Berkeley on the astatine work. First let us examine the further animal physiology and pathology. Acute lethal dose of ^{131}I was about 85 $\mu\text{Ci/g}$ (median lethal dose in 60 days), while that for astatine was only 1.12 $\mu\text{Ci/g}$ (Hamilton, Durbin, and Parrott 1954b). The amount of tissue destruction was large. At lower doses (e.g., 0.4 to 0.8 $\mu\text{Ci/g}$), the incidence of mammary tumors rose significantly in Sprague-Dawley rats beginning 135 days after a single intravenous injection (Hamilton, Durbin, and Parrott 1954c).

Accumulation of astatine by the human thyroid was measured in this period (Hamilton, Durbin, and Parrott 1954a,b). It was considerable—relatively higher than expected from the experiments employing rats. The uptake was related to the functional condition of the thyroid, much as is the uptake of radioiodine. Also, it seemed to be correlated with the amount of stable iodine already present in the gland. One patient with a thyroid tumor (papillary adenocarcinoma) was measured. There was no measurable accumulation of astatine in metastases to the lymph nodes from this tumor.

An interesting contrast between iodine and astatine was seen in the effect of an antithyroid drug like propyl thiouracil (Durbin, Hamilton, and Parrott 1954a).

(a) Actually about twenty isomers of astatine were identified. The one of most interest is ^{211}At . Astatine-210 has a convenient half-life also, but it decays to the very radiotoxic ^{210}Po (see chapter 4) and is thus useless for therapy. Astatine-211 has two modes of decay, one to stable ^{207}Pb through ^{211}Po , the other to ^{207}Bi and slowly (half-life fifty years) to stable ^{207}Pb .

Whereas uptake of iodine is greatly reduced or blocked by such drugs, the uptake of astatine was enhanced, in the rat at least. However, the contrast did not extend to the administration of thyroxine, where the two halogens behaved similarly (Shellabarger et al. 1954).

In the 1954 period, two UCRL reports on methodology were issued. One (Parrott et al. 1955) concerned the production and isolation of ^{211}At . The other (Durbin, Hamilton, and Parrott 1954b) concerned the codetermination of iodine isotopes and astatine in tissue.

Joe Hamilton presented a summary of the astatine story at the first Atoms for Peace Conference in Geneva, Switzerland, in June 1955 (Hamilton et al. 1955). There was no judgment made on its relative therapeutic potential.

Some interesting permutations of the astatine work were done in the succeeding years. For example, it appeared that permanent structural damage remained in the thyroid after astatine treatment, even though function, as measured by radioiodine uptake, had apparently returned to normal (Durbin et al. 1957). Durbin et al. (1958b) carried on with the animal work and produced a long and detailed study of the induction of tumors in the rat by ^{211}At . There were several varieties of mammary tumors, both benign and malignant, and tumors of the pituitary. The calculated radiation doses were on the order of 50 rad to mammary tissue and 240 rad to the pituitary. If multiplied by an appropriate RBE factor, these doses may have been sufficient to produce the tumors. However, the authors did not feel the information was sufficient for them to separate out a radiation effect from an endocrine effect and concluded it was both.

There was also considerable weight reduction of the ovary that was uniform regardless of treatments for the endocrine disturbances. Although the calculated radiation dose is not large, the authors felt this effect might be radiation-induced to some degree.

With the death of Joe Hamilton of leukemia in 1957 and the somewhat discouraging incidence of various forms of tissue damage, the work slacked off. Patricia Durbin, C. Willet Asling, and others of the team continued mechanistic studies, but there seems not to have been much push for any therapeutic trials. Asling et al. (1959) demonstrated that astatine concentrates in mammary tissue of the rat and is secreted in the milk. These phenomena occur also with iodine, and the authors do not speculate as to whether or not the evidence made them lean more toward a radiation origin of the tumors reported earlier.

In 1964, Dr. Durbin and workers at Columbia University joined forces for work on the pituitary tumors (Yokoro et al. 1964). They concluded that direct irradiation played a major role in the induction of these tumors.

Here the story ends. There was no formal statement that the toxicity of astatine discouraged its clinical use. Yet, it seems clear that we see here an instance where great promise for therapy was negated by undesirably high concentrations of the element in normal tissues and damage at relatively low doses when compared to the isotopes it was sought to improve upon.

4. Radiocolloids and Microspheres

In earlier chapters, we described the importance of the formation of colloids to the distribution of and site of the effects of radioactive materials. We saw that many radionuclides that exist as molecules or ions under their usual conditions of handling, e.g., low pH, absence of coupling agents, etc., were prone to undergo hydrolysis reactions and to form aggregates at the relatively high pH of body fluids. Since the RES, with cells located primarily in spleen, liver, bone

marrow, and the lymphatic system, regards these particles as foreign bodies, they are phagocytized and frequently sequestered in one or more of these organ systems. The toxic sequelae of such depositions are frequently referable to this process, as well as to trapping of large aggregates in blood vessels or lymphatics.

It is not surprising that these properties were looked upon as possible tools for medical uses of radionuclides. As the work on inorganic ions progressed, and few substances showed the remarkable ability of iodine to localize in tissue, the affinity of the RES for colloids looked more and more promising. It was not an easy way to go, for there were many problems. However, the usefulness, particularly for scanning, has grown to the point where for some organs, e.g., liver, radioactive colloids are among the most frequently used means for imaging and measuring blood flow.

Much of the work in the formative periods was domiciled in the AEC laboratories investigating radioisotope toxicology. Colloids were, of course, known and appreciated in biological systems in the 1930s, if not before. In addition to Thorotrast and thorium dioxide, there was interest in colloidal calcium phosphate, chromic phosphate, and many others. However, the overt use of colloids for localizing radiation doses began at Berkeley a bit before the end of World War II. Hardin Jones and colleagues from the Donner Laboratory described a method for distributing beta radiation to the RES in 1944 (Jones, Wrobel, and Lyons 1944). In 1949, the Berkeley group gave chemical principles and methods for the preparation of colloids of yttrium, zirconium, columbium, and lanthanum (Gofman 1949) and the controlled selective localization of these in bone marrow, liver, and spleen (Dobson et al. 1949).

Why were these rather unusual elements chosen? They have a tendency, like many elements in the rare earth group, to form colloids, and it was relatively easy to produce different types of colloids with them. Also, they possess among them (three yttrium isotopes, three zirconium isotopes, two columbium isotopes, and one lanthanum isotope) a variety of nuclear properties from pure beta emitters, through mixed beta-gamma emitters, to pure gamma emitters. The objectives of the work were both diagnostic and therapeutic uses.

It soon became apparent that particle size played an important role in both their localization and clearance. This is reminiscent of the large enterprise we reviewed in the chapter on inhalation toxicology. However, the interest here lay in blood clearance rates, rather than lung clearance. "Relatively large"^(a) colloids—as determined by presence of a Tyndall effect and laborious counting in a hemocytometer—tended to localize in liver and spleen. Very little got to bone marrow, probably because the liver and spleen screened out the particles. Isotopes of zirconium, columbium, and yttrium were most convenient for this use. The blood disappearance was characterized by an initial very rapid phase, followed by a slow phase with a half-life of over two hundred minutes (remember the similar behavior we saw in the toxicologic work?).

An "intermediate size" of both yttrium and zirconium could be prepared by fairly easy manipulations. Up to 60% of this left the blood so rapidly it was gone before the first blood sample could be taken. The rest left with a constant half-life of about forty-four to fifty-five minutes (up to seventy minutes of

(a) In those days, particle size distributions in aqueous systems were very difficult to quantitate except grossly by such measures as turbidity or counting on the microscope.

measurement). Liver was the primary deposition site for these, and bone marrow was second, ahead of spleen: In the case of yttrium, bone marrow was first.

The next steps are hard to follow. There was a gradual development. The uses of radiocolloids grew and extended. Ample detail can be found in the several textbooks and in the symposia cited (see, for example, the chapter by Muller [1965] from Switzerland in the Blahd textbook). The rare earths did not play as predominant a role as they did earlier. Instead, the emphasis was placed on radioactive colloidal gold^(a,b) and chromic phosphate. The former especially became very useful for direct application to sites of cancer because it remained in place almost indefinitely. Colloidal chromic phosphate was investigated in depth and used widely (Dobson et al. 1966). Ovarian tumors were treated extensively with radiocolloids by Muller, but many other localized tumors were also treated, especially palliatively.

Many workers preferred to have the radioactivity in an organic molecule that could be broken down more rapidly by tissue enzymes than the inorganic complexes. Rapid decomposition was especially desirable if the purpose was in-vivo counting by scanning techniques. Human serum albumin can be aggregated and labeled with various radionuclides, e.g., ^{131}I , ^{125}I , ^{51}Cr . The aggregation process is fairly simple, heat treatment and pH adjustment, and suspensions of particles from less than 10 to 200 μm (0.01 to 0.2 μ) in diameter are easily produced. A pioneer in this area was Dr. George Taplin. He worked early at the University of Rochester and for over three decades at the AEC Project at the University of California at Los Angeles (UCLA) and at the UCLA hospitals. He contributed many innovations to both nuclear medicine and radioisotope toxicology. He was keenly aware of the possible untoward effects of introducing aggregates that could block pulmonary or cerebral blood vessels. The UCLA group, along with others around the country, did fairly extensive animal experiments to check on the possibility of such complications. The early colloid preparations had fairly low specific activities, and the margin of safety as measured in the animal experiments was about fiftyfold. This was not considered enough to chance cerebral embolism, and clinical trials were deferred.

Henry Wagner at The Johns Hopkins University in Baltimore helped solve the problem by introducing aggregates with much higher specific activity (e.g., 1,000 μCi of ^{131}I per milligram of albumin). The developments at UCLA and at The Johns Hopkins are described in the chapter by Taplin et al. (1966).^(c) They checked out the possibility of cerebral complications in both dogs and monkeys and related it to the amount of material injected. By using the higher-specific-activity material (available commercially by then), the margin of safety for a lung

(a) Colloidal ^{198}Au preparations were first made by Paul Hahn (1956). A product of Dr. George Whipples's group at Rochester (chapter 5), Hahn went to Vanderbilt and later to Meharry Medical College. His book, *Therapeutic Use of Artificial Radioisotopes*, gives much important information on the development of the field.

(b) Seeds of radiogold were also used for implantation as a replacement for radon seeds (Henschke, James, and Myers 1953, 1954). This does not, of course, have anything to do with radiocolloids.

(c) Dr. George Taplin also did much pioneer work in lung diseases and knew a great deal about the development and uses of medical aerosols. He was a member of the inhalation toxicology panel of the original National Academy Committee on the Biological Effects of Atomic Radiation (BEAR); see chapter 16. He also developed methods for diagnosis of renal disease (see chapter 13 in Blahd 1965). His death in full career is a saddening note.

scan was considered to be greater than two thousand, assuming that less than 1 mg of aggregate was injected. The clinical work went ahead. Later clinical follow-ups at Harbor General Hospital in Los Angeles showed no objective or subjective reactions in over fifteen hundred scans. (The number is, of course, much greater now, but the techniques are different, as we will see in part B of this section.)

For greater localization in the bone marrow and less entrapment in liver and spleen, very small particle sizes are useful. Colloidal gold at $5\ \mu\text{m}$ ($0.005\ \mu$) has been suggested in treatment of chronic leukemia (Muller 1965). Naturally, the hazard of undesired trapping in blood vessels and embolism is further reduced by such a procedure. (Note that the particle sizes we are talking about here are very much smaller than those of most interest in inhalation toxicology—chapter 9.)

The Oak Ridge Institute of Nuclear Studies (now Oak Ridge Associated Universities), a separate entity from ORNL and financed indirectly by AEC and successor agencies through a consortium of universities, has long had a strong medical research program in both external radiation and radioisotopes. Partly because of nearness to the reactor and partly because of general interest, a fairly large program was developed on the rare earths (chapter 8). Some quite esoteric elements were checked out for possible uses in nuclear medicine, especially members of the lanthanide series, along with better known ones. The former included gadolinium, dysprosium, holmium, and lutetium. An excellent summary of the colloid chemistry involved and behavior of the colloids in animals can be found in a paper by Kyker and Rafter (1966) in the radio-pharmaceuticals symposium. It is of interest to note the extremely low concentrations at or above which immobilization of these elements is complete, viz., 10^{-7} mole/kg. All that is needed is to get it where it should stay!

For reasons that are not entirely clear, these entities did not find as much clinical favor as isotopes of gallium, on which the Oak Ridge Institute lavished concentrated attention. We will review this in a following section.

Finally, we come to the artificially produced plastic and ceramic microspheres. These were introduced in 1960. In chapter 9, we reviewed the use made of these (the plastic variety) in connection with the "hot particle" problem in inhalation toxicology. We mentioned that they were manufactured by the 3M Company in Minneapolis "for medical uses." The medical uses were to label the spheres and use them as tracers or for therapy in the way we have been discussing for colloids. They can be made in a large number of sizes and very high specific activities can be attained. Grotenhuis (1966) describes their properties and availability, and part of the discussion of the treatment of malignant disease with radiocolloids by Muller (1965) refers to their use. However, since they are essentially indestructible and would be around long after the radioactivity had decayed away, their use for diagnostic scans, which employs small amounts, may be preferable to the application of large amounts in therapy.

5. Radiophosphorus

The isotope ^{32}P was, as we have seen, among the earliest to be used for nuclear medicine and tracer chemistry. We need to say little more than we already have to be sure its position is made clear.

Since phosphorus is an integral part of most metabolic pathways, it is not surprising that it has a tendency to be labile. By today's criteria, ^{32}P is quite

energetic and of long half-life. Nevertheless, in addition to its early use for the treatment of leukemia and polycythemia vera, it has found use for tumor localization. Of interest is the fact that some types of thyroid nodules that fail to take up radioiodine do take up radiophosphorus. Many rapidly growing tumors can be differentiated from benign or slowly growing malignant tumors by their incorporation of radiophosphorus. Evidently, the metabolic pathways of some tumor types are especially demanding of phosphorylated intermediates.

On the treatment side, perhaps the history that is most pertinent to the period we are studying is the chapter by Shkurkin and Lawrence (1965) from Berkeley. As the work unfolded, the expectation for curing leukemia withered. Phosphorus-32 is not useful for acute leukemia. However, it is still used for some chronic types. The best results have continued to be with polycythemia vera, where treatment can be expected to result in a normal life expectancy. There is no question that the unwanted radiation dose to normal tissues has been one of the limiting factors for this radionuclide in other therapeutic modalities.

There are those who feel that long-term follow-ups for sequelae from the use of agents as powerful as ^{32}P have not been sufficient. Dr. Helen Woodard at Sloan-Kettering Institute in New York is one of these. In a personal letter to the author summarizing her long experience, she quotes many instances of severe bone marrow depression following use of ^{32}P , ^{35}S , etc. Sometimes treatment had to be suspended after what seemed to be rather small doses. While these effects are mild next to many of the really toxic radionuclides we have reviewed in this book (the microcurie doses of ^{32}P used would have been fatal with an element like plutonium), Dr. Woodard quotes an instance of aspermia in a man who received $310\ \mu\text{Ci/kg}$ of ^{32}P in six months, even though he had only mild and transitory bone marrow depression. The aspermia occurred *nine* years after the exposure. While there are too many other possible causes to be sure the ^{32}P treatment did it, Dr. Woodard urged much more careful follow-up procedures over long periods (Woodard 1971). This is an underinvestigated part of radioisotope toxicology.

Finally, although the toxicologic aspects are important to us, the story of ^{32}P also raises many more basic questions. Whether a given tumor type takes up the radionuclide or not is, at present, unpredictable except by a vague linkage to rate of growth. It is a commentary on the complexities of tumor biology and our knowledge of the basic biochemical processes that we must still be essentially empirical in these matters.

6. Gallium

We devote space in this section on specifics in the 1948 to 1966 period to gallium, not because of its paramount importance to either tracer chemistry or nuclear medicine, but because it occupied the attention of many AEC and related workers in the radioisotope toxicology field. Gallium was proposed for use as a reactor coolant at Oak Ridge (Hayes 1966), and radioisotopes of it were readily available there. In the late 1940s, Dudley and coworkers (Dudley, Maddox, and La Rue 1949; Dudley, Imirie, and Istock 1950) found that gallium (the nuclide ^{72}Ga) concentrated where new bone was being formed and thus might be a good marker for tumor sites and even a therapeutic agent. The results of both diagnostic and therapeutic trials at the then-new Oak Ridge Institute of Nuclear Studies (later Oak Ridge Associated Universities) and the Oak Ridge Hospital were, however, disappointing (Brucer, Andrews, and

Bruner, and others 1953; King, Brady, and Dudley 1952; Dudley, Markowitz, and Mitchell 1956). Despite localization in tumor sites, even before roentgenographic changes were evident, the therapeutic results were not consistent. Also, the photons from ^{72}Ga were too energetic for efficient scanning.

Later, interest in gallium was rekindled by the introduction of a generator "Cow" that produced ^{68}Ga from ^{68}Ge . This isotope has a sixty-eight minute half-life, and it decays primarily by positron emission. It found use when chelated with EDTA (see chapter 19) as a brain-scanning agent and in the citrate form with added stable gallium as a carrier for bone scanning (Edwards and Hayes 1972). However, the need for the carrier (to produce adequate skeletal uptake) generated concern for potential chemical toxicity, and there was considerable retention in the gut. Acceptance was therefore not widespread.

Still later, another isotope of gallium, ^{67}Ga , attracted interest (Comargo et al. 1979). When given intravenously as the citrate, this radionuclide seemed to localize in the lesions of Hodgkin's disease (Edwards and Hayes 1972). It has a longer half-life than ^{68}Ga , viz., seventy-eight hours and does not require a carrier. It seemed to be free of untoward side effects.

The primary reason for interest in these gallium isotopes was their uptake by tumors—again in a very selective fashion. Furthermore, ^{68}Ga showed considerable nonspecific uptake by inflamed or infected tissues. Acute pyogenic abscesses are the most consistent in taking up ^{67}Ga . This has turned out to be a useful diagnostic tool for ascertaining by scanning techniques, the location of hidden pockets of infection. These uses have eclipsed the original idea of treating bone tumors with ^{72}Ga and provide an instance where toxicity interdicted one use but led to modifications of nuclides and their use for something else.

As with ^{32}P , we are left with the uncomfortable conclusion that we must be empirical about determining what type of tissue will take up the isotope and what type will not. The basic work to make such differences predictable is a challenge for the future.

The gallium work did give us, besides a diagnostic agent, much information on the role of carriers—such as we saw in earlier chapters. The tissue distribution can be quite different when the isotope is in the carrier-free state (^{67}Ga) or in the presence of carrier, or, as in the case of ^{72}Ga , at low specific activity, which means a higher concentration for the same radiation dose. As Hayes (1966) discussed, the amount in liver and spleen is quite different in carrier-free than in the carrier-present state.

7. Antibodies—The Immunologic Approach

We introduced the principles of this approach to therapy with radioisotopes in section I C of this chapter. The exquisite specificity of antibodies for cell and tissue types encouraged extensive laboratory investigations to try to work out the right system. The requirements are stiff. The antibody should preferably be specific for the malignant cells at issue. It must be possible to get it to the site, sometimes through barriers. The compound must be amenable to the process of labeling with a suitable radioisotope and not be too easily degraded by the radiation field required to deliver a therapeutic dose.

Our space permits a consideration of only two major projects attacking this problem: the one at the University of Rochester headed by William F. Bale, Irving L. Spar and their colleagues, already mentioned; and the project at the Roswell Park Memorial Institute located in Buffalo, New York, headed by David Pressman. The first was funded almost entirely by AEC, with a bit of help in the

last years from the National Cancer Institute. The second was not so clearly an activity of people who had formerly worked in radiation toxicology and radiation biophysics as had Dr. Bale and his group. It had support from several sources.

The Rochester work got started when Dr. Bale returned from his year of duty at AEC Headquarters, where he was concerned with many problems of radiation protection, including the uranium miners (see chapter 3). It took considerable courage to embark on an entirely new and complex field totally different from the instrumentation and biophysics that had been Bale's forte for many years.^(a) He soon persuaded Dr. Irving Spar, who had just completed a Ph.D. in biology with a thesis in genetics with immunological overtones, to join him. Later, Dr. Ralph Helmkamp, an organic chemist with much experience in synthetic organic chemistry, retired from his long-held post in the chemistry department at Rochester and joined Bale's group to undertake the difficult problems of labeling the complex antibody molecules. In addition, the group acquired an exceptionally capable set of technical associates and collaborators. Most of the group spent the rest of their scientific careers on this one problem.

A complete and informative review of the entire field, to the date of writing, was placed in one of the volumes in the series, *Advances in Biological and Medical Physics* (Bale and Spar 1957). The production of antibodies with "substantial organ and tissue specificity" is described. The preparation of antibodies against kidney, adrenal, lymphatic tissue, several other organs, and tumors is described in depth. Also described is the methodology for labeling antibodies with radioisotopes; usually ^{131}I . Much of the early antitumor work utilized anti-Walker tumor antibodies.

It was not easy going. Localization of labeled (iodinated) anti-Walker preparations was preferential for adrenal, ovary, liver, and spleen.^(b) The localization was a function of time, but there was always too much in blood and tissues other than tumor in these early experiments. Thus, too much of the activity was remaining in circulating blood, with resultant dose to tissues other than the tumor.

It was suggested that exclusion from the circulation of certain parts of the body not containing tumor might increase the relative dose to the tumor tissue. This would require complex procedures for isolation of segments of the circulation—not beyond the abilities of vascular surgery, but not to be undertaken lightly. It was also suggested that some of the information being obtained on protection of tissues against radiation by preparations from spleen, bone marrow, etc., might be used to increase the ratio of effectiveness for tumor versus other organs, despite the presence of unwanted radioactivity in the blood.

The work at Rochester continued well into the 1970s. There was concentration on fibrinogen and immunological uses of derivatives of it. However, this carries us further than we can go. The accumulating results were encouraging

(a) William F. Bale received the first Ph.D. degree given in Biophysics at the University of Rochester. At that time, it was an interdepartmental degree and included departments from the College of Arts and Sciences as well as the Medical School.

(b) Results are summarized in the review cited. Individual papers can be seen in the *Journal of Immunology*, several symposia, the *Proceedings of the Society for Experimental Biology and Medicine*, and University of Rochester Atomic Energy Project reports. Some are cited in the review.

enough to permit a few clinical trials. However, on balance, the degree of localization, as in so many other potential therapeutic procedures of these decades, was not sufficient for generalized therapeutic use. In the interim, a great deal was learned about the immunological processes investigated.

After his retirement in 1976, Dr. Bale went to the Georgia Institute of Technology, where he tried a different approach. We will review his ideas briefly in section IV C.

The Roswell Park work was largely immunological and concerned, among other things, antibodies against chemically induced rat hepatomas. It utilized ^{125}I in pair with ^{131}I for labeling purposes and autoradiography. The latter was important because the sites of antibody localization in tumor could be investigated at the cellular level.^(a)

A vignette of the problems of the field can be seen in a quotation from the Roswell Park work in the *Journal of Nuclear Medicine* in 1964 (Yagi and Pressman 1964). "...the localization of control protein or antibody is unpredictably variable in different tumors of the same individual or even different parts of individual tumors, depending on vascularity, stage of development, etc." (Yagi and Pressman 1964).

This somewhat pessimistic outlook set the pace for the field for many years. However, very recent (1980s) developments in immunology indicate it may be possible to increase localization greatly, and the field may be due for a resurgence (Cronkite 1982).

There were, of course, numerous uses of radioactively labeled antigens in both basic research and studies of pharmacodynamics (e.g., Korngold et al. 1953). However, these have not changed the general conclusions inherent in what we have seen thus far. But we should not forget that the tracer uses of labeled materials in immunology underlay the development of the extremely powerful tool, radioimmunoassay (to be discussed briefly in a later section).

8. Neutron-Capture Reactions as Therapeutic Tools

The principle involved in neutron-capture reactions is the production of radioisotopes *in vivo* by localization, preferably at a tumor site, of substances with high cross sections for neutron capture, and subsequent irradiation by a flux of slow neutrons. Likely substances to place *in situ* are ^{10}B , ^6Li , and ^{235}U . The first two produce alpha particles and a residual nucleus on capture of a slow neutron; ^{235}U fissions with release of considerable energy (162 MeV). The advantage of such a system is that there is no radiation until the external neutron beam is turned on, and it can be localized by the *collimation* and focus of the beam as well as by specific attachment of the fissionable substance. The problem is, as always, preferential localization of the substance in the tumor cells.

In the chapter on uranium (chapter 2), we examined briefly the collaborative effort between Dr. William Sweet of MGH and the Boston Veterans Administration Hospitals, and members of the Health Physics Division of ORNL using ^{235}U (see also Hursh and Spoor 1973, pp. 204-206). While the interest was partly in following the metabolism of the higher-specific-activity isotopes of uranium in man, the work also provided an opportunity to try the *in-situ* neutron-capture therapy. As we saw in chapter 2, the results were marginal.

(a) The Bale-Spar review gives thirteen references to Pressman's work.

At about the same time, Sweet appears to have also considered the use of boron (Sweet and Javid 1952). This was followed through a collaborative effort with Dr. Lee Farr, the first director of the Medical Division at BNL, which was then relatively new, and his collaborators (Farr 1955; Farr et al. 1954). Boron-10 was found to localize to some extent in the brain because it did not pass the blood-brain barrier. It was reasoned it might localize in tumor tissue of the brain enough to warrant a trial. A few patients seriously ill with brain tumors were given boron and then irradiated as locally as possible with a somewhat mixed neutron beam taken from the old graphite reactor at Brookhaven.^(a) Despite some evidence of localized effects, the results were discouraging. Too much boron remained in the blood (Cronkite 1982), and this was activated to carry radiation to many sites away from the one hoped-for localization. Also, the neutron beam was far from pure or easy to focus.

Bale and Spar allude to use of antibodies to carry ^{10}B or other isotopes useful for neutron-capture therapy. They calculated the degree of localization of the added isotope in the antibody needed to produce the desired dose in the region of antibody localization. For boron, each antibody molecule should have twenty-seven ^{10}B atoms attached. For ^6Li , the required number is seventy-three. Only for ^{235}U is the number small: 3.3 ^{235}U atoms per antibody molecule. Thus, we needed not only localization of the antibody at the tumor site, but attachment of sufficient atoms to capture the neutrons effectively.

Despite the problems of the early work, even the conclusion that the treatment may have made these particular patients worse, if anything, the development of reactors for medical uses continued. There were many reasons to think the techniques could be greatly refined and improved. Also, reactors could do many other things. Brookhaven eventually built a medical reactor, which has served for many years, but not predominantly for neutron-capture therapy. By this time, Lee Farr had gone elsewhere, but his pioneering ideas and those of his associates should not be discounted.

We will see some possible and some tested extrapolations to a much later period in section IV C. However, as part of this first era of *therapeutic intent*, we must conclude that the old bugaboo of selective localization put the neutron activation work on ice for many years. It did not inhibit very large advances in the tracer chemistry and basic science facets of the field.

9. Comments on the Earlier Years

Obviously, these were years of rapid progress. The workers and institutions identified with radioisotope toxicology played major roles in initiating, furthering, and controlling the safety of the developments. Radioactive isotopes became as commonplace in the clinical departments and in institutions devoted entirely to clinical medicine as they had been in biomedical research. By the middle of the decade of the 1960s, the impetus for new therapeutic uses began to wane, even though there was no paucity of ideas for isotopes, physical and chemical forms, and applications to therapy. A good overview of the status of *therapy* with radioactive isotopes at the end of this period can be seen in a 1968 review paper in the *Progress in Atomic Medicine* series by Wasserman and Glass (1968), Mount Sinai Hospital and School of Medicine. The portion of their summary table that concerns internal applications is reproduced as table 20.5.

(a) It was a somewhat heroic experiment since the patient had to be lifted to the top of the reactor in most unhospital-like surroundings.

A glance back through the developments we have cited in this section gives perspective on the large contribution of the major radioisotope centers supported by the AEC, the Manhattan Project, and, to a lesser degree, other government agencies in getting the work started and perpetuated.

TABLE 20.5. Isotopes Used in Therapy as of 1968

I. External Applications		
A. Teletherapy—External Gamma Ray Beam Units		
Cobalt-60		External beam therapy; deep-seated and other malignancies
Cesium-137		
Radium-226		
B. External Beta Radiation Units		
Strontium-90		Widespread superficial malignancies
C. Extracorporeal Irradiation Units		
Gamma: Cobalt-60, Cesium-137		Induction of lymphocytopenia and immuno-suppression; treatment of chronic leukemia
Beta: Strontium-90		
D. Interstitial, Intracavitary and Contact Therapy with Encapsulated Gamma Ray Sources		
Radium-226	Tantalum-182	Implantation of accessible malignant tumors, e.g., carcinoma of the cervix, carcinoma of the bladder, lymph-node metastases
Radon-222	Iridium-192	
Cobalt-60	Gold-198	
Cesium-137		
E. Interstitial Therapy with Isotopes Decaying by Electron Capture		
Iodine-125	Cesium-131	Implantation of tumors
F. Contact (Superficial) Therapy with Encapsulated Beta Sources		
Phosphorus-32	Sulfur-35	Treatment of selected dermatologic and ophthalmologic conditions
Strontium-90	Cerium-144	
G. Interstitial Therapy with Encapsulated Beta Sources		
Strontium-90	Phosphorus-32	Local tissue destruction, e.g., hypophysectomy, cordotomy, etc.
Yttrium-90	Gold-198	
II. Internal Applications		
A. Metabolic (Selective) Localization		
1. Isotopes administered in inorganic chemical form		
Iodine-131		Thyroid disorders, angina pectoris
Phosphorus-32		Polycythemia vera, chronic leukemia, thrombocythemia, osseous metastases
Sulfur-35		Chondrosarcoma
(Sodium-24)		Leukemia
(Strontium-90)		Malignancies of bone and bone marrow
(Calcium-45, 47)		Malignancies of bone and bone marrow
(Gallium-72)		Malignancies of bone and bone marrow
(Arsenic-76)		Chronic leukemia
2. Other forms		
Chelates—Yttrium-90		Immunosuppression; polycythemia vera; myeloma
Drugs—Tritium tagged		Malignant tumors
Neutron Capture Therapy—Boron-10		Glioblastoma multiforme

TABLE 20.5. Continued

B. Physical (Paraselective) Localization		
1. Intravascular administration		
a. Radiocolloids (intravenous administration)		
Phosphorus-32	Chronic leukemia; lymphoreticular malignancies	
Gold-198		
Yttrium-90		
b. Ceramic microspheres (intra-arterial, isolation-perfusion)		
Yttrium-90	Malignant tumors	
Phosphorus-32		
c. Short-lived beta-emitters (isolation-perfusion technique)		
Scandium-49		
Zinc-69	Malignant tumors	
Dysprosium-165		
2. Intracavitary administration		
Radiocolloids		
Phosphorus-32	Malignant pleural and peritoneal effusions, palliation and prophylaxis	
Yttrium-90		
Gold-198		
3. Interstitial administration		
Radiocolloids		
Phosphorus-32	Carcinoma of the prostate, cervix and breast; other malignancies	
Yttrium-90		
Gold-198		
4. Intralymphatic administration		
Radiocolloids		
Phosphorus-32		
Gold-198	Lymphoreticular malignancies, carcinomas, melanoma; palliation and prophylaxis	
Radioiodinated (Iodine-131) radiographic contrast material (Ethiodol, Lipiodol)		
5. Intra-articular administration		
Radiocolloids		
Gold-198	Recurrent synovial effusions	

Source: Reset from Wasserman and Glass 1968. Reprinted by permission of Grune & Stratton, Inc., Orlando, Florida, and the author, copyright 1968.

B. The Later Years—The Era of Ever More Scanning and Ever Shorter Half-Lives

There is obviously no sharp demarcation between the periods I have chosen to consider as eras. Many developments that underlay the second era began in the late 1950s and early 1960s, even before (Prinzmetal et al. 1949). Some were soon adopted and were expanding rapidly even by 1966. Nevertheless, the changing flavor of the enterprise was especially noticeable by the time of the symposium on radioactive pharmaceuticals at Oak Ridge, in the nature of the reports in the fast-growing *Journal of Nuclear Medicine* and the meetings of its Society, and in the symposia organized to look at new developments after the mid-1960s. As in the first era, many of the major developments came from laboratories supported by AEC or the U.S. PHS. However, their influence was more at the

beginning, less into operations of the 1980s, since nuclear medicine is now a major part of medicine and has much support from fees, third-party billings, and the like.

The *raison d'être* for the developments of this era, let us emphasize again, was reduction of the radiation dose to the patient. Thus, toxicologic considerations were the chief motivation. Increases in speed and convenience were the second major factor in the developments.^(a)

In this section, we will trace those developments of most pertinence to the central theme of this chapter and this book. We will see that therapy with radioisotopes played a more minor role in the planning—even though a few procedures continued to be of life-saving significance.

1. More Radioiodine

It was natural in these later years for there to be considerable concentration on the development of new isomers of iodine. We will review these in this section. However, as will be clear, these years saw iodine lose its place of supremacy to other, even more convenient, radionuclides.

At the June 1960 meeting of the Society of Nuclear Medicine held at Estes Park, Colorado, Dr. William G. Myers of Ohio State University suggested that ^{125}I should have significant advantages over ^{131}I for in-vivo scanning in thyroid-function studies. The lack of beta particles in its unique mode of decay (x rays plus Auger and internal conversion electrons) could result in considerable reduction (about one-half) in radiation dose. The dose rate was also reduced because of its longer half-life (sixty days).^(b) Yet, very adequate energies were available for tracing metabolic pathways of stable iodine. The abstract (Myers and Vanderleeden 1960a) was followed almost immediately by a complete paper (Myers and Vanderleeden 1960b) from the Departments of Medicine, Physiology and Radiology at the University Health Center and the Department of Physics of The Ohio State University. The ^{125}I could be obtained by bombardment of tellurium or antimony in a cyclotron. Some was produced by neutron bombardment in a reactor. The cited paper gives full details of generation, properties, and uses.

The low energies involved made this iodine isotope very suitable for labeling various compounds that had previously been labeled with ^{131}I .

A "merit ratio"^(c) could be calculated to highlight the advantages of ^{125}I over ^{131}I . Using 6.3 cm beneath the surface as the optimal distance, the merit ratio on the basis of relative photon energy was 3.7; on the basis of the quantum efficiency of the detector (100% for ^{125}I versus 50% for ^{131}I), it was 2.0; and the merit ratio based on the background counts in the particular detectors used (250 cpm for ^{131}I versus only 9.3 cpm for ^{125}I when shielded with a few millimeters of copper) was 27. Myers and colleagues multiplied these separate ratios to get a combined "merit" ratio of 200 for ^{125}I over ^{131}I .^(d)

(a) Tracer chemistry, of course, benefited also from some of the changes wrought. However, the primary changes were for increased convenience, speed, and accuracy of procedures already in place, not a shift in emphasis.

(b) Which also meant a more convenient "shelf" time.

(c) Ratio of usable signals to energy absorbed locally.

(d) Obviously, not all of this is resident in the isotope itself. Some is in the instrumentation that can be applied. It might be even better at less than 6.3 cm, gradually less as the depth of the source in tissue increases.

By the time Myers was named a Nuclear Medicine Pioneer^(a) by the Society of Nuclear Medicine (Wagner 1981), hundreds of millions of ^{125}I tests were being performed worldwide each year. A large number of these involve radioimmunoassay procedures for, as we will see, $^{99\text{m}}\text{Tc}$ was beginning to make inroads on the uses of iodine for in-vivo scanning.

At the Deutscher Röntgenkongress in 1964, Myers presented an excellent summary of the development and uses of ^{125}I in the period 1960 to 1964 (Myers 1965). This includes a reasonably complete literature summary, useful since this was, of course, not an Ohio State monopoly; along with extensive descriptions of ^{125}I 's special uses in labeled organic molecules.

However, Myers was not about to stop at ^{125}I . In May 1962, he described in collaboration with Hal Anger of the Donner Laboratory at Berkeley the virtues for scanning in nuclear medicine for ^{123}I . The radiation dose from this isotope in quantities suitable for diagnostic scans was only about 5% of that from ^{131}I (Myers and Anger 1962). This isotope has a thirteen-hour half-life. Therefore, its "shelf" time is less advantageous than ^{125}I 's. However, this difference in half-life is useful for double-labeling purposes. Also, it permits serial administration, and its 159-keV gamma ray is quite advantageous for scanning (see also Harper et al. 1963).

Unfortunately, ^{123}I was not then easily available in sufficient quantities and purity to supplant ^{125}I . An earnest effort was made to develop facilities that could meet the needs. This was part of the mission of the new biomedical cyclotrons such as the one at UCLA. At the dedication of this facility, Professor Glenn Seaborg (whom we met extensively in earlier chapters) included these statements:

Perhaps one of the most important medical isotopes this cyclotron will be making is iodine-123. . . There is no question about the utility of iodine-123. The question is whether enough can be produced in the present target-cyclotron configuration and then rapidly extracted for conversion into pharmaceutically suitable forms. If this alone can be accomplished, AEC's investment of men, machines and time shall have been a major success.
(Seaborg 1971)^(b)

For further detail of other isotopes of iodine (e.g., ^{121}I and ^{123}I), the reader is referred to Myers's historical and analytical summary given at the Oak Ridge symposium on radioactive pharmaceuticals (Myers 1966b) and to specific descriptions (Myers 1966a and 1974b). Here criteria are assigned for an ideal radioisotope in terms of the merit ratio for in-vivo diagnostic applications. The author does not single out one or even a few isotopes for special recommendation. Apparently, it is left for future developments to make these judgments.

Myers's historical review is also full of references to work by others. He worked closely with Professor I. Perlman, codiscoverer of ^{123}I and ^{121}I , with Hal Anger on ^{123}I and with others at the Donner Laboratory during the tenure of a visiting appointment to Berkeley arranged by Professor John Lawrence. It is

(a) In this honor he joined, among others, George Hevesy, Irène Curie, Ernst and John Lawrence, Lise Meitner, and his close and dear friend, Paul Aebersold.

(b) The expectations were met by the UCLA cyclotron in the early years. However, as commercial instruments became more numerous, active large users such as UCLA found it cheaper to rely on them. The local instrument could thus be reserved for research uses (Bennett 1979, 1981).

obvious, also, that close cooperation existed with the Isotopes Development Center at ORNL.

Although the orientation was medical, quite obviously the entire isotope establishment was involved. The health and medical physicists got interested too because of the potential for dose reduction. Note, for example, work by Sayeg and Preston (1973)^(a) given at a Health Physics Society Midyear Topical Symposium, "Health Physics in the Healing Arts." Also, the uses of these substances as tracers in all of biology received attention from the Feinendegen group already cited in connection with transmutation problems (Ertl, Feinendegen, and Heiniger 1970). Recently, the microdosimetric aspects of damage in DNA by ^{125}I have been investigated (Martin and Haseltine 1981).

Thus, despite the introduction of many new entities and techniques, the iodine isotopes maintained a predominant position for many years. The motivation, let us again be reminded, has been primarily reduction of patient dose, i.e., avoiding toxicity.

2. Nuclide Generators—Technetium Rises to Prominence

Even with the abundance of radioisotopes made available in the earlier years through the Isotopes Division of AEC, there were problems with the short-half-life isotopes. They either decayed away before they could be used or had to be dispatched at such high activities that shielding and shipping were major problems. With the pressure for more and more short-half-life material for diagnostic uses, the application of nuclide generators grew considerably.

The idea of a nuclide generator is, of course, old. The classic example is the separation of 3.8-day ^{222}Rn to make radon seeds from the 1,620-yr ^{226}Ra , accomplished by Failla in 1926. During World War II, application was made of shipping 12.8-day ^{140}Ba as a source of 40.2-hr ^{140}La . In principle, any short-lived daughter (24-hr or less half-life) coupled to a parent of half-life suitable for generating the daughter in reasonable quantity over a useful time period could become a nuclide generator. However, several criteria must be met (after Colombetti and Palma 1978):

1. It must yield a daughter with high radiochemical and radionuclide purity.
2. It must be safe and simple to operate.
3. It must be sterile and pyrogen free.
4. The product must be convenient for the preparation of radiopharmaceuticals.
5. It must be capable of multiple separations.
6. The daughter should have a half-life less than 24 hr. Otherwise, the radionuclide is better obtained directly from a commercial source.

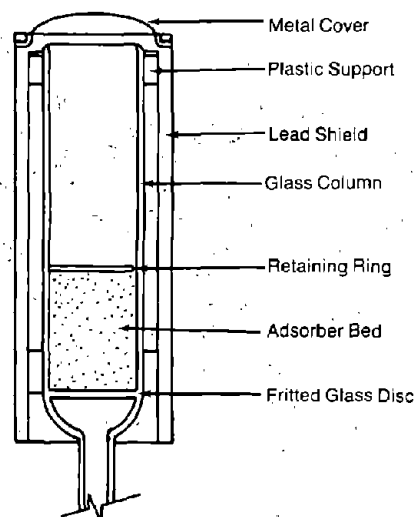
A diagram of a very simple system is given as figure 20.7. This open system is primarily a laboratory type. Commercial systems are sealed to prevent entrance of bacteria into the column. They are tapped by fitting a closed container of sterile eluting solution and having a millipore filter in line with the outlet.

The absorber bed may be alumina, a Dowex resin, alumina with silica, etc. All of these rest in part upon the isotope separations techniques developed under the MED and carried forward postwar by the AEC. Few isotope pairs contain a gas phase, which made possible the first isotope generator—radon from radium.

(a) University of Kentucky Medical Center, Department of Radiation Medicine.

For obvious reasons, the process involved has been called milking, and the generators have been called "cows."

FIGURE 20.7. A chromatographic column used in open generator systems. Later systems were closed and sterile. (Redrawn from Richards 1966a.)



The first commercial application with real convenience was developed at BNL in 1954 for the ^{132}Te - ^{132}I system (cited by Richards 1966a). This was used more in Europe than in the United States, since 2.3-hr iodine did not catch on here. Brookhaven was instrumental in developing several other systems. The most widely used is the generator for 6-hr $^{99\text{m}}\text{Tc}$ from the parent, 2.7-day ^{99}Mo . Indeed, $^{99\text{m}}\text{Tc}$ soon made rapid inroads on iodine for many uses, since it has very favorable nuclear properties. Technetium was introduced for thyroid and other scans by Harper et al. (1964) as the pertechnetate. It emits no beta radiation, and the dose to the patient is quite low. Its use has grown enormously in the last two decades.^(a) A $^{99\text{m}}\text{Tc}$ generator is described in detail by Richards (1966b). The facility has the appearance of a large commercial production facility, and it was indeed used to supply national needs for a while.

Listings of generator systems in use in the mid-1960s, and those expected by Richards to be useful in the future, are given as table 20.6A and B. A "cow" for ^{68}Ga was developed by Yano and Anger (1964) because of the usefulness of positrons in the developing instrumentation.

It will be noted that the genesis of these devices goes well back into the period we have called "The Earlier Years." We place the discussion here because it was in the later years that the short-lived isotopes really came into their own. The development hinged considerably on parallel advances in measuring instruments. Together with accelerators, these generators made the later years a different era.

3. Accelerators

In the introduction to this chapter, we mentioned the current trend back toward accelerator-produced isotopes. This is occurring partly because of the interest in ultra-short half-life isotopes. Even the nuclide generator falls short of needs if the daughter isotope decays away too rapidly. Also, there are only a limited number of nuclide couplets suitable for such systems. Accelerators are much more versatile.

(a) The diagnostic era, as we know it today, can be said to have developed in earnest from this point, and the credit goes first to Harper (University of Chicago). Bennett (1982) stated that about 90% of routine nuclear medicine procedures now involve $^{99\text{m}}\text{Tc}$.

TABLE 20.6A. Generator Systems*

Daughter Isotope	Half-Life	Parent Isotope	Half-Life	Applications
^{28}Al	2.3 min	^{28}Mg	21.3 hr	Aluminum tracer
^{137}Ba	2.6 min	^{137}Cs	30 years	Dynamic studies
^{68}Ga	68 min	^{68}Ge	280 days	Positron scanning and bone studies
^{132}I	2.3 hr	^{132}Te	3.2 days	Thyroid studies and double tagging
^{140}La	40.2 hr	^{140}Ba	12.8 days	
$^{87\text{m}}\text{Sr}$	2.8 hr	^{87}Y	80 hr	Bone scanning
$^{99\text{m}}\text{Tc}$	6 hr	^{99}Mo	67 hr	Scanning: brain, thyroid, etc.
^{90}Y	64 hr	^{90}Sr	28 years	Therapy

* Commercially available or have been used for special purposes.

TABLE 20.6B. Potential Generator Systems

Daughter Isotope	Half-Life	Parent Isotope	Half-Life
^{72}As	26 hr	^{72}Se	8.4 days
^{131}Cs	9.7 days	^{131}Ba	11.6 days
$^{113\text{m}}\text{In}$	1.7 hr	^{113}Sn	118 days
^{42}K	12.4 hr	^{42}Ar	>3.5 years
^{144}Pr	17.3 min	^{144}Ce	285 days
$^{103\text{m}}\text{Rh}$	57 min	^{103}Pd	17 days
^{44}Sc	3.9 hr	^{44}Ti	~10 ³ years
$^{125\text{m}}\text{Te}$	58 days	^{125}Sb	2.7 years
^{127}Te	9.3 hr	$^{127\text{m}}\text{Te}$	105 days

Source: Modified from Richards 1966a.

In August 1977, the Bureau of Radiological Health of the U.S. Food and Drug Administration (FDA) produced the report of a task force on short-lived radionuclides for medical applications (HEW-FDA 1977). The task force looked hard at many of the known and suspected long-term sequelae of uses of isotopes like ^{131}I and took up the need for larger quantities of short-lived isotopes, already discussed. In an appendix, they list twenty-eight sites where cyclotrons exist capable of producing radionuclides of medical interest. Most of these are in large institutions with support from AEC, the Energy Research and Development Administration (ERDA), DOE, and from the Department of Health, Education, and Welfare (HEW). A few are in industry or smaller academic institutions. Without implying that these machines were not all contributing what they might to the medical sphere, the mere act of listing them undoubtedly brought attention to bear on their potential.^(a)

(a) Some were, as we have seen, already fully devoted to medical uses. Others were only peripherally applied to medicine. In the early years, for example, the Ohio State cyclotron devoted every Monday to producing medical isotopes. However, in the first shipment from the Oak Ridge reactor, they received 350 mc of ^{32}P , more than they could have produced in a whole year. So it is not quantity but quality and short half-life that underlie our interests in accelerator-produced isotopes.

Meanwhile, in Berkeley, a physicist named Alan Fleischer communicated to Bill Myers that he and some others were about to establish a company to build cyclotrons chiefly for medical uses. They were encouraged by Dr. Myers and, as luck would have it, Myers spent part of the first years of his retirement using the first machine built by the company. It was installed some years earlier at the Sloan-Kettering Institute in New York and constituted the beginning of a trend away from complete dependence on government for such devices.^(a) However, the field could never have developed without the strong support of government and collaboration among the medical, basic science, and toxicologic groups.

Laughlin, Tilbury, and Dahl (1971) at Sloan-Kettering Memorial Institute give a useful summary of cyclotrons for medical uses. There may be some difference of opinion on when and where the first fully medical cyclotron appeared. We have remarked several times on the orientation to medical and biological uses surrounding the Berkeley machines in the early Radiation Laboratory and the Crocker Laboratory, but these machines did many other things; ditto for the machine at MIT. We can be assured that potential biomedical uses, particularly in cancer research, were prominently displayed in the funding proposals for nearly all of the machines listed in the HEW-FDA report cited above. It is commonly stated that the first cyclotron built entirely for medical uses was at the Hammersmith Hospital in the United Kingdom under the stimulus of L. H. Gray. Since this machine was in a hospital and not part of a general university facility, it may well warrant the title. In the United States, machines of similar purposes and characteristics appeared at Washington University in St. Louis and elsewhere (Laughlin, Tilbury, and Dahl 1971).

Myers, the consistent visionary, believes nearly all large hospitals will someday have small cyclotrons to make his "twinkling" atoms (Myers 1981b). The cost of such machines is being drastically reduced but is still substantial, even in modern-day medicine. When chided by some less enthusiastic surgical colleagues, Myers retorts with, "How much did your operating room cost?" (Myers 1981a).

There seems little doubt but the availability of radioactive isotopes with very short half-lives and suitable energies for scanning makes predictions for still more growth quite reasonable. At the Dallas meeting of the Society for Nuclear Medicine in 1976, there were over two hundred papers using cyclotron-produced isotopes. The idea had obviously grown and spread.

4. Instrumentation and Methodology

We have called this period the "Era of Ever More Scanning and Ever Shorter Half-Lives." The dependence on new sources of isotopes *in situ* is now obvious. In this section, we will look very briefly at the measurement and recording side. Not described to any extent in this chapter, but seen earlier (chapter 17), were the basic instrument and methodologic developments. Started in the major national laboratories, even the MED, the development gradually shifted to private industry during these years. Many manufacturers produced instruments for health physics, tracer chemistry, and nuclear medicine as part of diversified

(a) It was hardly a complete change from dependence on government, only a change of *modus operandi*. Bennett (1981) stated that the United States paid for the machine.

operations. Others began to specialize. The instrumentation for the era we are now in has become not only very complex but very specialized.

The generic term "scanning" (or "imaging") was applied to these devices and processes. The early approach was to place a Geiger counter over the area to be measured as in the now-classic picture reproduced as figure 20.6. This gave no spatial orientation except by hand movement of the counter. It gave essentially a count rate or an integral count over a selected period.

As interest developed in counting organs besides the thyroid, many of them much larger, the labor of moving the counter by hand—and the inaccuracies involved—led to the development of mechanical scanners. These could be programmed to cover a series of coordinates and, thus, were "rectilinear scanners."

The first successful rectilinear scanner was developed by Benedict Cassen in 1951 working at UCLA (Cassen et al. 1951). It was very useful as was its successor designs. Indeed, it made enough difference to the practice of nuclear medicine that the original is now in the Smithsonian Institution. Yet they had their limitations.

An entirely different device, first described under the simple title "Scintillation Camera," was introduced by Hal Anger at the University of California at Berkeley (Anger 1958). This device could view the entire field without moving, but the field was somewhat limited, and for a while the mechanical scanner had greater sensitivity. However, developments came rapidly. Anger, who was described by Wagner (1981) on the occasion of an award as "a convergence of nuclear physics, electronics, optics and information handling," described the scintillation camera at the second Atoms for Peace Conference in Geneva, Switzerland (Anger 1959), and improvements came in rapid succession (Myers 1979).

A device developed at The Ohio State University and called the "Gammicon" was something of a hybrid. It used a scintillation detector and a calcium tungstate crystal (not sodium iodide as in the later devices), but for the scans it utilized the Teledeltos system devised by the Western Union Company to transmit pictures by wire (Mueller and Myers 1955).

Obviously, a large advantage of the scintillation camera is the ability to present dynamic states such as blood flow, dye movement, and related measurements.

The steps in development of these and other devices is nicely summarized in the Nuclear Medicine Pioneer Citation-1974 for Hal Oscar Anger, D.Sc. (Hon.) in the *Journal of Nuclear Medicine* for June 1974 (Myers 1974a). The early (1952) gamma-ray camera had a 3-mm pinhole in a lead shield and needed concentrations of ^{131}I of about a millicurie per square-centimeter area for reliable detection. The much more sensitive version of the scintillation camera came about five years later. By 1963, an 11.5-in. crystal was employed. Much is said about the matching of isotope with camera. Anger also developed the multiplane tomographic gamma-ray scanner and a whole-body scanner. No single individual seems to have invented and developed so many measuring devices for nuclear medicine; and it was all done from one of AEC's most consistently supported laboratories.

It took a few years for commercial developers to decide these devices had a future. There was also a considerable period during which there was debate as to the relative merits of camera versus mechanical scanners. Also, there were problems about patents and much red tape. Further detail is beyond our scope, except to mention that the present instrumentation embodies the best features of all systems, including computerized operation and printout or display. The

debate now seems (in the mid 1980s) to be around digital versus analogue systems, a long step from the early Geiger tubes.

In 1979, the Office of Health and Environmental Research of DOE reported the work of a study group appointed to examine nuclear medicine instrumentation development (DOE 1979). This added to a report in 1976 from an ERDA/NIH task force. It commented on the importance of continued instrumentation development to both biomedical research and the diagnosis of disease. It recommended substantially increased support for instrumentation research and development and a stable, long-term commitment of support for established research groups. It also urged effective means of technology transfer among the basic and applied physics, chemistry, and engineering programs and with NIH programs. The task group did not concur with the view that nuclear medicine may have reached the stage where innovation and product improvement could be expected entirely from the commercial sector. Thus, a continuing role of government in this enterprise, which could never have gotten started without government support, is urged by this blue-ribbon panel. Particular emphasis was placed on assurance of technical feasibility and clinical efficacy before undertaking commercial development. Undoubtedly, this view does not prevail at present, but the arguments are well worth examining.

Finally, the role of the synthetic chemist should not be forgotten. An important part of the methodologies of this second era is the development of ever more specific compounds to help direct the new short half-life isotopes to desired areas or for desired functional measurements. While not quite up to the specificity we can expect in an antibody system, many radioactive pharmaceuticals are significantly advanced. However, these considerations are getting us too far afield to warrant description, except to say that many of the ideas started in the institutions we have become familiar with.^(a)

C. A Possible Third Era

Despite the many discouragements toward finding broad applications for the therapeutic uses of radioisotopes, the research did not halt altogether. Ideas kept springing up that showed promise enough to be funded by the NIH or in part (especially earlier) by AEC, ERDA, and DOE. At least two are directly related to approaches and people we have already described. A third, therapy with beams of particles from facilities like the Meson facility at Los Alamos, is really not a radioisotope technique. Even though these beams contain particles of high-LET and are thus related to much of our discussion of alpha emitters, we must leave their discussion for others.

The first extension to consider is that developed by Bill (Dr. William F.) Bale (see section IV A 7). We look at it first because, unfortunately, it is now completed, except for publication of work in progress. Dr. Bale, a long and dear friend to this author, died in Atlanta in mid-1982.

There was a powerful source of ^{90}Sr at the Georgia Tech Medical Research Foundation where Bale went after his retirement from Rochester. He and his colleagues (especially Angela de los Angeles Contreras) could milk this source

(a) The money has come in recent years from very diverse sources. For example, it is said that investment funds for the so-called "CAT Scanner" came from the singing group, the Beatles!

for the decay product, ^{90}Y . This could be adsorbed onto ion exchange resin microspheres, separated, and incinerated to become carbon microspheres about $15\ \mu$ in diameter.^(a) This size would lodge in capillaries of an organ like liver into which they could be placed by the surgeon (an Atlanta surgeon named Grady did much of this work) using a catheter in the hepatic artery. By chance, the liver tumors of interest get most of their circulation from the hepatic artery, even though the whole organ gets about two-thirds of its blood from the portal vein. The combination of anatomical localization of the microspheres and the hard beta ray of ^{90}Y conferred many potential advantages.

Along with this work with microspheres, Bale expanded his earlier work with antibodies as carriers of radioactivity. Again we must give the work short shrift here, except to indicate that it may be ready for a new sprint of activity somewhere using monoclonal antibodies, which have localization potential even greater than the conventional antibodies used in work such as that done by Bale and his group (Cronkite 1982; Sutherland 1988).

The second potential development that may usher in a new era of therapeutic interest is located primarily at Brookhaven and in Japan, with some work at other installations including Georgia Tech. This may eventually hinge on coalescence of several of the approaches worked out earlier.

Even though neutron-capture therapy seemed dead in 1961, by 1966 it was revived by development and use of an epithermal (i.e., above thermal) neutron beam rather than the thermal beam used in the original Brookhaven and MIT work. One of the problems with thermal beams is their rapid (and exponential) attenuation in tissue and the consequent high dose to surface tissues. Fairchild and Goodman (1966) at Brookhaven and Columbia University determined that tumors deeper than 2.5 cm could not be treated with a thermal beam, even with the best attainable localization of ^{10}B in the tumor. Potential advantages of factors up to 1.9 could be predicted at all depths greater than 1.5 cm with the epithermal beam from the Brookhaven Medical Research Reactor. Work with phantoms was helpful but not really exciting without better localization of the boron or some other neutron-capturing element.

In the intervening years, much was done to improve the dose localization possible with epithermal neutron beams from reactors like, but not limited to, the one at Brookhaven. Also, the development of much better carriers to localize the boron received much attention and encouraging development (Fairchild 1982a). At the International Symposium on the Synthesis and Applications of Isotopically Labeled Compounds held in Kansas City, Missouri, in June 1982, Fairchild (1982b) considered the dosimetric implications for beams of epithermal neutrons of a sulfhydryl boron hydride and of borated analogues of chlorpromazine, thiouracil, porphyrins, amino acids, and nucleosides. Only the first has been used clinically: $\text{Na}_2\text{B}_{12}\text{H}_{11}\text{SH}$,^(b) and it has been used primarily in Japan by Dr. H. Hatanaka.

(a) The microspheres were originally prepared by the 3M Company (Grotenhuis 1966; see section IV A 7), but the labor of being certain absolutely no ^{90}Sr contaminated the ^{90}Y ran the cost and problems up so much that the Atlanta group decided to do the preparations themselves (Bale 1979).

(b) It is called a "second generation" compound of boron by investigators. Earlier water-soluble pentaborates used by Farr, Sweet, et al. were considered "first generation."

The Japanese work has been going on since 1968 and has concentrated on glioma (brain tumor) patients. It is a fairly heroic treatment since craniotomy (removal of a section of the skull) and surgical removal of all accessible tumor tissue were routine, followed by radio- and chemotherapy and neutron activation therapy. The craniotomy provided much more favorable depth-dose conditions for the epithermal neutron beam than would otherwise have been the case. The combination therapy (i.e., sulfhydryl boron hydride and epithermal neutron beam following conventional surgery and other therapy) has now been tried on fifty-three patients (Fairchild 1982a). There have been some "cures" lasting eight to nine years, a very significant increase for the usually rapidly fatal glioblastoma. A summary of twelve years of experience in Japan has been provided by Hatanaka et al. (1982).

The quest for other compounds that would carry the boron or other elements with high neutron capture cross sections has not reached the point of clinical application, in the United States at least. The compounds described by Fairchild might be considered "third generation" boron-carrying compounds. So far, the enhancement of dose from epithermal neutrons has been confined to work with phantoms. Procedures for borating antibodies have been developed and as many as two thousand boron atoms placed on each antibody molecule. (Remember that Bale and Spar's calculations indicated twenty-seven ^{10}B atoms should be enough.) However, specificity and adequacy for neutron capture therapy remain to be demonstrated. Enthusiasm is high, particularly for monoclonal antibodies (Cronkite 1982; Fairchild 1982a; Sutherland 1988). It would indeed be important if a combination of the techniques that have alone produced marginal results produced a significant therapeutic advance.

Other ideas should be mentioned. One harks back to getting a labeled compound more specifically to a tumor. The Brookhaven group (Fairchild et al. 1982) have found that thiouracil gets incorporated into the biosynthetic pathway of melanin as a false precursor and remains bound. Absolute uptake of labeled thiouracil by mouse melanoma was relatively high. Tagging with ^{35}S is contemplated since such a compound is available commercially. This *might* be almost as specific as iodine in the thyroid.

Another is the use of the spontaneously fissionable ^{252}Cf . The potentials for this radionuclide were described with enthusiasm by Seaborg in 1973, as part of a general compendium on possible medical uses of transuranium elements (Seaborg 1973). The fission produces an enormous local dose. Localization of ^{252}Cf to tumor sites has not been an easy task.

Another new idea harks back to the advantages of ^{125}I . Here the ^{125}I is made in situ by introducing into DNA a thymidine analog (deoxyuridine was best) that had been labeled with stable iodine (^{127}I). The bound iodine was then photoactivated with 33- to 60-keV monoenergetic photons. This produces ^{125}I with all its advantageous Auger electrons, etc., in a very localized manner and avoids the presence of ^{125}I radiations in other areas. Obviously, the idea is comparable to neutron activation but employs photoactivation. The Brookhaven group is especially enthusiastic about this approach (Fairchild, Brill, and Ettinger 1982).

Only the future can tell whether or not these ideas, which seem very promising, will spark a recrudescence of interest in new therapeutic applications of radioisotopes. They seem sufficiently promising, and sufficiently adherent to the maxim of reducing the unwanted radiation dose to normal tissues, to warrant attention here. It is unlikely that this third era, if it does develop, will see any decrease in the diagnostic uses of radioisotopes in nuclear medicine. At most,

it would mean a possible broadening of the therapeutic uses with no letup in the scanning, development of short half-life isotopes, and of ever better instrumentation.^(a)

I have chosen developments from selected laboratories close to the radioisotope toxicology enterprise. There are, of course, many others. However, the examples should show how the contributions from former AEC, ERDA, and currently DOE and PHS laboratories have continued to advance nuclear medicine despite retrenchment of support. Fortunately, support from agencies such as the NIH has stepped in for some of the most interesting and promising developments. It is a lively and fascinating field.

V. Summary and Commentary

Quite obviously, we cannot hope to present a detailed history of nuclear medicine and tracer chemistry in a volume that, like this one, is devoted to other areas. Yet, the research and the investigators concerned with health effects of radioactive materials have been, and always will be, closely related to both nuclear medicine and tracer chemistry. In fact, they have common roots, as was detailed in chapter 5. Frequently, two or more aspects can be found in the same individual. To further delineate these interrelationships, the chapter begins with a mock genealogy. This includes the locales that could be regarded as the "old homestead" for the family of disciplines.

For the first time in this long book, a formal discussion of dosage calculations is introduced. This is commonly referred to as "internal dosimetry" since it concerns radiation doses from internally deposited radionuclides. The delay in introducing dosimetry was so that the MIRD system, developed primarily for nuclear medicine and by practitioners of nuclear medicine, could be discussed side-by-side with the classical system usually attributed to Marinelli, Quimby, and Hine, with important later contributions by Snyder. Only a few detailed illustrations are given since other sources expound internal dosimetry in depth. Yet, it is hoped they provide the reader with a grasp of the concepts and the types of information needed.

Even in the 1930s, medical uses of radioisotopes, for both diagnosis and therapy, were undertaken. The relatively limited supply of radioisotopes, their short half-life, and problems of purification confined these early efforts to large installations handy to an accelerator. During World War II, the medical-use effort was severely truncated, partly by lack of supplies and partly by occupation of the same personnel with the new potential health problems of the nuclear age detailed in this book. Soon after the close of the war, particularly under the stimulus of the Atoms for Peace Program, supplies of radioisotopes became almost unlimited, and nuclear medicine began its meteoric rise that still continues. Tracer chemistry required relatively less material and seemed to grow even during the war years because of the tremendous power of the technique.

The effects of radiation and radioactivity at the cellular level and their mechanisms constitute a major portion of the field of radiobiology. The applications to nuclear medicine and the perfection of tracer techniques added measurably

(a) That there has been no letup is demonstrated by the very recent book by Bragg, Rubin, and Youker (1985) under the title *Oncologic Imaging*. The subtitle states, "Oncologic imaging is saving lives." Also, the monoclonal antibody has stimulated full-scale international meetings (Sutherland 1988).

to knowledge of cell effects gained from other sources. The chapter reviews some of the highlights of these.

Specific applications of radionuclides in medical practice can be discussed conveniently in two basically different contexts—diagnosis and therapy. The earliest work considered diagnostic tests but was soon followed by attempts at therapeutic uses. In the decades of the late 1940s through the middle 1960s, the hopes for making order-of-magnitude advances in cancer therapy guided much of the work. Diagnosis was not neglected, but the spotlight was on therapy. Manipulations of carriers were legion. All of them had the purpose of increasing the relative dose to tumor tissue and reducing that to normal tissue. These manipulations included use of radiocolloids, microspheres, attaching the radioactive material to specific antibodies, *in situ* neutron capture techniques, and others. Naturally, new isotopes with more desirable properties were tried also. However, the results did not live up to expectations. The age-old problem of specificity, *i.e.*, killing the target cells with minimal effects on normal cells, brought disappointment after disappointment. Now, a few standard therapeutic modalities are commonly used as a result of all of these efforts, but only a few.

As techniques for measurement of radioactivity and for scanning specific anatomical areas, either statically or dynamically, advanced, so did the uses of radionuclides for diagnostic tests. Pharmaceuticals were developed that had great specificity for localizing in areas of interest. Also, shorter half-life radioisotopes appeared in pure form that could be incorporated into the radiopharmaceuticals and greatly reduce the dose to the patient. Thus, the period from the mid-1960s to the present is dubbed, herein, an era of ever more scanning and ever shorter half-lives.

Toward the end of the chapter, some current advances are described that may produce a revival of interest in uses of radionuclides for therapy.

The constant role of potential unwanted health effects has perforce been emphasized in the chapter. There can be no doubt but the health benefits of the uses of radioisotopes under the aegis of practitioners of nuclear medicine have been enormous and far outweigh any demonstrable untoward side effects. This is particularly true for the diagnostic uses. It is incontrovertibly true for the researches aided by tracer techniques. Nevertheless, the workers in the field of diagnostics and their compatriots concerned with possible toxicologic effects have had to be guided in all of their developments by balancing effectiveness and delivery of the lowest possible dose to the patient. In therapy, the dictum has been likewise the production of the minimum unwanted dose to normal tissue while delivering an effective dose to the target cells. These two considerations have put many a technique on the shelf. The duality attests, as stated at the outset of the chapter, to the close relation between the major branches of the family of workers concerned with the biomedical aspects of radionuclides.

References

- Aebersold, P. C. 1948. Availability of isotopes. In *The use of isotopes in biology and medicine*, pp. 56-79. Madison, Wisc.: Univ. of Wisc. Press.
- Aebersold, P. C. 1956. The development of nuclear medicine. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* 75:1027-39.
- Anger, H. O. 1958. Scintillation camera. *Rev. Sci. Instrum.* 29:27-33.
- Anger, H. O. 1959. Mapping the distribution of gamma-ray emitting isotopes with the scintillation camera. In *Progress in nuclear energy*, eds. W. G. Marley and K. Z. Morgan, vol. 1 ser. 12, pp. 189-92. New York-London: Pergamon Press.

- Asling, C. W., P. W. Durbin, M. E. Johnston, and M. W. Parrott. 1959. Demonstration of the concentration of astatine-211 in the mammary tissue of the rat. *Endocrinology* 64:579-85.
- Atkins, H. L., J. S. Robertson, B. Y. Croft, B. Tsui, H. Susskind, K. J. Ellis, M. K. Loken, and S. Treves. 1980. Estimates of radiation absorbed doses from radioxenons in lung imaging. MIRD dose estimate report no. 9. *J. Nucl. Med.* 21:459-65.
- Baily, N. 1982. Personal communication, Univ. of Calif., San Diego.
- Bale, W. F. 1979. Personal interview, Atlanta, Ga., November 5-6, 1979.
- Bale, W. F. and I. L. Spar. 1957. Studies directed toward the use of antibodies as carriers of radioactivity for therapy. In *Advances in biological and medical physics*, eds. J. H. Lawrence and C. A. Tobias, vol. 5, pp. 285-356. New York: Academic Press.
- Baserga, R., H. Lisco, and W. E. Kisielski. 1966. Tumor induction in mice by radioactive thymidine. *Radiat. Res.* 29:583-96.
- Bennett, L. R. 1979. Taped interview at Univ. of Calif., Los Angeles, February 8, 1979.
- Bennett, L. R. 1981. Personal interview.
- Bennett, L. R. 1982. Personal communication, September 1982.
- Berger, M. J. 1968. Energy deposition in water by photons from point isotropic sources. MIRD pamphlet no. 2. *J. Nucl. Med. Suppl.* 1:15-25.
- Berger, M. J. 1971. Distribution of absorbed dose around point sources of electrons and beta particles in water and other media. MIRD pamphlet no. 7. *J. Nucl. Med. Suppl.* 5:5-23.
- Bianchi, P. A., A. R. Crathorn, and K. V. Shooter. 1962. The use of tritium-labelled thymidine in studies of the synthesis of deoxyribonucleic acids. In *Tritium in the physical and biological sciences*, vol. 2, pp. 269-76. Proceedings of a symposium held in Vienna, May 3-10, 1961. Vienna: International Atomic Energy Agency.
- Blaht, W. H., ed. 1965. *Nuclear Medicine*. New York: McGraw-Hill.
- Bond, V. P. and L. E. Feinendegen. 1966. Intranuclear ^3H thymidine: Dosimetric, radiobiological and radiation protection aspects. *Health Phys.* 12:1007-20.
- Bond, V. P., T. H. Flidner, E. P. Cronkite, J. R. Rubini, G. Brecher, and P. Schork. 1959. Proliferation potentials of bone marrow and blood cells studied by in vitro uptake of thymidine- H_3 . *Acta Haematol.* 21:1-15.
- Bragg, D. G., P. Rubin, and J. E. Youker. 1985. *Oncologic imaging*. New York-Oxford: Pergamon Press.
- BRH-NTIS. See Bureau of Radiological Health.
- Brodsky, A. 1970. Discussion [of Johnson's paper]. In Johnson 1970.
- Brookhaven National Laboratory. 1948. *Symposium on radioiodine, July 28-30, 1948*. AECU-51, BNL-C-5. Oak Ridge, Tenn.: U.S. Atomic Energy Commission, Technical Information Division.
- Brooks, A. L., A. L. Carsten, D. K. Mead, J. C. Retherford, and C. R. Crain. 1976. The effect of continuous intake of tritiated water (HTO) on the liver chromosomes of mice. *Radiat. Res.* 68:480-89.
- Brownell, G. L., W. H. Ellett, and A. R. Reddy. 1968. Absorbed fractions for photon dosimetry. MIRD pamphlet no. 3. *J. Nucl. Med. Suppl.* 1:27-39.
- Brucer, M. 1978. The genesis of thyroid-radioiodine (or how Robley Evans became a super-salesman before he had a product to sell). *Vignettes of Nucl. Med.*, no. 19. St. Louis: Mallinckrodt, Inc.
- Brucer, M., G. A. Andrews, and H. D. Bruner. 1953. A study of gallium 72 : Summary and conclusions. *Radiology* 61:534-36. [This study includes the following: M. Brucer and H. D. Bruner. I. Physics and radiation characteristics of gallium 72 , 61:537-43; J. D. Perkinson, Jr., J. S. Eldridge, and B. M. Cooper. II. Gallium chemistry of biological interest, 61:543-45; J. D. Perkinson, Jr. and R. S. Ingols. III. Effect of internal irradiation on respiration of rat liver slices, 61:545-50; H. D. Bruner, B. M. Cooper, and D. J. Rehbock. IV. Toxicity of gallium citrate in dogs and rats, 61:550-55; H. D. Bruner, J. D. Perkinson, Jr., E. R. King, G. A. Andrews, J. B. Nash, and M. Brucer. V. Distribution studies on gallium 72 in rats, 61:555-70; G. A. Andrews, S. W. Root, and H. D. Kerman. VI. Clinical studies with gallium 72 , 61:570-88; H. D. Bruner, J. Gray, S. W. Root, and

- M. Brucer. VII. Studies of the urinary excretion of gallium⁷² in man, 61:588-90; M. Brucer, G. A. Andrews, D. J. Rehbock, S. W. Root, and J. Gray. VIII. Autopsy studies of distribution of gallium⁷², 61:590-95; J. C. Gallimore, Jr., G. A. Boyd, G. A. Andrews, and M. Brucer. IX. Autoradiographic studies, 61:595-602; H. D. Bruner, R. L. Hayes, and J. D. Perkinson, Jr. X. Preliminary data on gallium⁶⁷, 61:602-13.]
- Bruner, H. D., E. R. King, and M. P. Smyser. 1951. *Tables to correct for physical decay of some frequently used isotopes*. ORO-26. Oak Ridge, Tenn.: Oak Ridge Institute of Nuclear Studies.
- Bureau of Radiological Health. 1970. *Radiological health handbook*. Springfield, Va.: National Technical Information Center. [Reprint of revised edition of handbook, PB-230 846.]
- Burki, H. J. and S. Okada. 1968. A comparison of the killing of cultured mammalian cells induced by decay of incorporated tritiated molecules at -196°C. *Biophys. J.* 8:445-56.
- Carsten, A. L. 1979. Tritium in the environment. In *Advances in radiation biology*, vol. 8, pp. 419-58. New York: Academic Press.
- Casarett, A. P. 1968. *Radiation biology*. Englewood Cliffs, N.J.: Prentice-Hall.
- Cassen, B., L. Curtis, C. Reed, and R. Libby. 1951. Instrumentation for ¹³¹I use in medical studies. *Nucleonics* 9(2):46-50.
- Chapman, E. M. 1965. Treatment of hyperthyroidism with radioactive iodine. Chapter 24 in Bland 1965, pp. 617-41.
- Charlton, J. C. 1966. Problems characteristic of radioactive pharmaceuticals. Chapter 2 in *Radioactive pharmaceuticals*, eds. G. A. Andrews, R. M. Kniseley, and H. N. Wagner, CONF-651111, pp. 33-50. Proceedings of a symposium held at Oak Ridge Institute of Nuclear Studies, November 1-4, 1965. Springfield, Va.: National Technical Information Service.
- Cleaver, J. E., G. H. Thomas, and H. J. Burki. 1972. Biological damage from intranuclear tritium: DNA strand breaks and their repair. *Science* 177:996-98.
- Cloutier, R. J. and E. E. Watson. 1973. Radiation doses from nuclear medicine procedures. In *Health physics in the healing arts*, DHEW pub. (FDA) 73-8029, pp. 71-78. Proceedings of the Health Physics Society topical symposium held in San Juan, Puerto Rico, December 1972. Washington, D.C.: U.S. Dept. of Health, Education, and Welfare.
- Cloutier, R. J., E. E. Watson, and J. L. Coffey. 1978. Radiation dosimetry. Chapter 7 in *Textbook of nuclear medicine: Basic science*, eds. A. F. G. Rocha and J. C. Harbert, pp. 126-45. Philadelphia, Pa.: Lea and Febiger.
- Cohn, W. E. 1948 and 1980. Toxicity of inhaled or ingested radioactive products. *Nucleonics* 3(1):21-26. Reprinted as a landmark paper with comments by J. N. Stannard in *Health Phys.* 38:1015-20.
- Cole, J. W. and A. McKalen. 1961. Observations of cell renewal in human rectal mucosa *in vivo* with thymidine-H³. *Gastroenterology* 41:122-25.
- Cole, J. W. and A. McKalen. 1963. Studies on the morphogenesis of adenomatous polyps in the human colon. *Cancer* 16:998-1002.
- Colombetti, L. and T. Palma. 1978. Radionuclide generator systems. Chapter 10 in *Textbook of nuclear medicine: Basic science*, eds. A. F. G. Rocha and J. C. Harbert. Philadelphia, Pa.: Lea and Febiger.
- Comargo, E., G. Johnston, S. Larsen, and H. Wagner, Jr. 1979. Whole body scanning with gallium-67. Chapter 16 in *Textbook of nuclear medicine: Clinical applications*, eds. A. F. G. Rocha and J. C. Harbert, pp. 443-55. Philadelphia, Pa.: Lea and Febiger.
- Cronkite, E. 1982. Personal taped interview at Brookhaven National Laboratory, September 15, 1982.
- Cronkite, E. P., T. M. Flidner, S. A. Killmann, and J. R. Rubini. 1962. Tritium-labelled thymidine (H³ TDR): Its somatic toxicity and use in the study of growth rates and potentials in normal and malignant tissue of man and animals. In *Tritium in the physical and biological sciences*, vol. 2, pp. 189-209. Proceedings of a symposium held in Vienna, May 3-10, 1961. Vienna: International Atomic Energy Agency.
- Department of Energy. 1979. *Nuclear medicine instrumentation development: DOE program*. DOE/EV-0034. Washington, D.C.: U.S. Department of Energy.

- Department of Health, Education and Welfare, Food and Drug Administration. 1977. *The developing role of short-lived radionuclides in nuclear medicine*, DHEW pub. (FDA) 77-8035. Report of a task force to the Bureau of Radiological Health, FDA. Washington, D.C.
- Deus, S. F. and J. W. Poston. 1976. The development of a mathematical phantom representing a 10-year old for use in internal dosimetry calculations. In *Proceedings of a symposium on radiopharmaceutical dosimetry*, DHEW pub. (FDA) 76-8044. Oak Ridge, Tenn.: Oak Ridge Associated Universities.
- Deus, S. F., V. Provenzano, and W. S. Snyder. 1977. Specific absorbed fractions for photons emitted in the walls of the GI tract. *Health Phys.* 33:191-97.
- Dewey, W. C., R. M. Humphrey, and B. A. Jones. 1965. Comparisons of tritiated thymidine, tritiated water, and cobalt-60 gamma rays in inducing chromosomal aberrations. *Radiat. Res.* 24:214-38.
- DHEW-FDA. See Department of Health, Education and Welfare, Food and Drug Administration.
- Dillman, L. T. 1969. Radionuclide decay schemes and nuclear parameters for use in radiation-dose estimation. MIRD pamphlet no. 4, *J. Nucl. Med. Suppl.* 2:5-32.
- Dillman, L. T. 1970. Radionuclide decay schemes and nuclear parameters for use in radiation-dose estimation, Part 2. MIRD pamphlet no. 6. *J. Nucl. Med. Suppl.* 4:5-32.
- Dobson, E. L., L. J. Finkelstein, C. R. Finney, and L. S. Kelly. 1966. Particulate chromic phosphate: Colloid characteristics suitable for measurement of liver circulation. Chapter 27 in *Radioactive pharmaceuticals*, eds. G. A. Andrews, R. M. Kniseley, and H. N. Wagner, CONF-651111, pp. 477-502. Proceedings of a symposium held at Oak Ridge Institute of Nuclear Studies, November 1-4, 1965. Oak Ridge, Tenn.: U.S. Atomic Energy Commission.
- Dobson, E. L., J. W. Gofman, H. B. Jones, L. S. Kelly, and L. A. Walker. 1949. Studies with colloids containing radioisotopes of yttrium, zirconium, columbium, and lanthanum II. The controlled selective localization of radioisotopes of yttrium, zirconium, and columbium in bone marrow, liver, and spleen. *J. Lab. Clin. Med.* 34:305-12.
- DOE. See Department of Energy.
- Dudley, H. C., G. W. Imirie, and J. T. Istock. 1950. Deposition of radiogallium (Ga^{72}) in proliferatory tissues. *Radiology* 55:571-78.
- Dudley, H. C., G. E. Maddox, and H. C. La Rue. 1949. Studies of the metabolism of gallium. *J. Pharmacol. Exp. Ther.* 96:135-38.
- Dudley, H. C., H. A. Markowitz, and T. G. Mitchell. 1956. Studies of the localization of radioactive gallium (Ga^{72}) in bone lesions. *J. Bone and Joint Surg.* 38-A:627-37.
- Durbin, P. W., J. G. Hamilton, and M. W. Parrott. 1954a. Effect of pretreatment with propyl thiouracil on accumulation of astatine-211 by thyroid gland of the rat. *Proc. Soc. Exp. Biol. Med.* 86:369-71.
- Durbin, P. W., J. G. Hamilton, and M. W. Parrott. 1954b. *The codetermination of iodine-127, iodine-131, and astatine-211 in tissue*. URCL-2792. Berkeley, Calif.: Univ. of Calif. Radiation Laboratory.
- Durbin, P. W., C. W. Asling, M. E. Johnston, and J. G. Hamilton. 1957. The effect of propyl thiouracil on the recovery of rat thyroid gland from irradiation with astatine-211. *Anat. Rec.* 129:17-37.
- Durbin, P. W., C. W. Asling, M. E. Johnston, and J. G. Hamilton. 1958a. Long term sequelae of massive doses of I^{131} in rats. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* 79:1010-25.
- Durbin, P. W., C. W. Asling, M. E. Johnston, M. W. Parrott, N. Jeung, M. H. Williams, and J. G. Hamilton. 1958b. The induction of tumors in the rat by astatine-211. *Radiat. Res.* 9:378-97.
- Durbin, P. W., G. D. Barr, M. H. Williams, N. Jeung, and M. E. Johnston. 1961. Estimation of radiation dosage delivered by a single massive injection of I^{131} in the rat. *Radiat. Res.* 14:149-66.

- Edwards, C. L. and R. L. Hayes. 1972. Localization of tumors with radioisotopes. In *Clinical uses of radionuclides: Critical comparison with other techniques*, eds. F. A. Goswitz, G. A. Andrews, and M. Viamonte, Jr., CONF-711101, pp. 618-39. Proceedings of a symposium held at Oak Ridge Associated Universities, November 15-19, 1971. Springfield, Va.: National Technical Information Service.
- Ellett, W. H., A. B. Callahan, and G. L. Brownell. 1964. Gamma-ray dosimetry of internal emitters: Monte Carlo calculations of absorbed dose from point sources. *Br. J. Radiol.* 37:45-52.
- Ellett, W. H. and R. M. Humes. 1971. Absorbed fractions for small volumes containing photon-emitting radioactivity. MIRD pamphlet no. 8. *J. Nucl. Med. Suppl.* 5:25-32.
- Emerson, C. H. and L. E. Braverman. 1980. Thyroid irradiation—One view. *N. Engl. J. Med.* 303:217-18.
- Ertl, H. H., L. E. Feinendegen, and H. J. Heiniger. 1970. Iodine-125, a tracer in cell biology: Physical properties and biological aspects. *Phys. Med. Biol.* 15:447-56.
- Evans, R. D. 1948. Fundamentals of radioactivity and its instrumentation. In *Advances in biological and medical physics*, eds. J. Lawrence and J. Hamilton, vol. 1, pp. 151-221 [especially p. 185]. New York: Academic Press.
- Fairchild, R. 1982a. A taped personal interview at Brookhaven National Laboratory, September 16, 1982.
- Fairchild, R. 1982b. Dosimetric implications of new compounds for neutron capture therapy (NCT). In *Proceedings of an international symposium on the synthesis and applications of isotopically labeled compounds*. Held in Kansas City, Mo., June 6-11, 1982.
- Fairchild, R. G., A. B. Brill, and K. V. Ettinger. 1982. Radiation enhancement with iodinated deoxyuridine. *Invest. Radiol.* 17:407-16.
- Fairchild, R. G. and L. J. Goodman. 1966. Development and dosimetry of an "epithelial" neutron beam for possible use in neutron capture therapy II. Absorbed dose measurements in a phantom man. *Phys. Med. Biol.* 11:15-30.
- Fairchild, R., S. Packer, D. Greenberg, P. Som, A. Brill, I. Fand, and W. McNally. 1982. *Thiouracil distribution in mice carrying transplantable melanoma*. BNL 82-141. Upton, N.Y.: Brookhaven National Laboratory.
- Farr, L. E. 1955. Experimental application of neutron capture therapy to glioblastoma multiforme. *Acta Unio Int. Contra Cancrum* 11:500-504.
- Farr, L. E., W. H. Sweet, J. S. Robertson, C. G. Foster, H. B. Locksley, D. L. Sutherland, M. L. Mendelsohn, and E. E. Stickley. 1954. Neutron capture therapy with boron in the treatment of glioblastoma multiforme. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* 71:279-93.
- Feinendegen, L. E. and V. P. Bond. 1973. Transmutation versus beta irradiation in the pathological effects of tritium decay. In *Tritium*, eds. A. A. Moghissi and M. W. Carter, CONF-710809, pp. 221-31. Proceedings of a symposium held in Las Vegas, August 30-September 2, 1971. Phoenix and Las Vegas: Messenger-Graphics.
- Ford, M. R., W. S. Snyder, and G. G. Warner. 1975. Variation of the absorbed fraction with shape and size of the thyroid. *Health Physics Division annual report period ending June 30, 1975*. ORNL-5046, pp. 207-13. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Ghelelovitch, S. 1969. Cancérologie—Comparaison, chez la drosophile, des effets tumorigènes des uridines tritiées soit en position 5, soit en position 6. *C. R. Hebd. Séances Acad. Sci., Ser. D—Sci. Nat.* 268:237-39.
- Gofman, J. 1949. Studies with colloids containing radioisotopes of yttrium, zirconium, columbium, and lanthanum I. The chemical principles and methods involved in preparation of colloids of yttrium, zirconium, columbium, and lanthanum. *J. Lab. Clin. Med.* 34:297-304.
- Greenfield, M. A. 1965. Radioisotope dosimetry. Chapter 5 in Blahd 1965, pp. 93-122.

- Grotenhuis, I. M. 1966. Properties and uses of radiating microspheres. Chapter 11f in *Radioactive pharmaceuticals*, eds. G. A. Andrews, R. M. Kniseley, and H. N. Wagner, CONF-651111, pp. 205-9. Proceedings of a symposium held at Oak Ridge Institute of Nuclear Studies, November 1-4, 1965. Oak Ridge, Tenn.: U.S. Atomic Energy Commission.
- Hahn, P., ed. 1956. *Therapeutic use of artificial radioisotopes* [especially pp. 365-74]. New York: John Wiley & Sons.
- Hamilton, J. G. 1941. The application of radioactive tracers to biology and medicine. *J. Appl. Physiol.* 12:440-60.
- Hamilton, J. G., P. W. Durbin, and M. W. Parrott. 1954a. Accumulation of astatine²¹¹ by thyroid gland in man. *Proc. Soc. Exp. Biol. Med.* 86:366-69.
- Hamilton, J. G., P. W. Durbin, and M. Parrott. 1954b. Comparison of acute and chronic changes produced in rats by iodine-131 and astatine-211 at lethal levels. Preliminary clinical data on the uptake of astatine-211 in patients with thyroid disease. Chapter 24 in *Proceedings of the 2d radioisotope conference*, pp. 219-31. Held in Oxford, July 19-23, 1954. London: Butterworth Scientific Publications.
- Hamilton, J. G., P. W. Durbin, and M. Parrott. 1954c. The accumulation and destructive action of astatine²¹¹ (eka-iodine) in the thyroid gland of rats and monkeys. *J. Clin. Endocrinol. & Metab.* 14:1161-78.
- Hamilton, J. G. and M. H. Soley. 1940. A comparison of the metabolism of iodine and of element 85 (eka-iodine). *Proc. Natl. Acad. Sci.* 26:483-89.
- Hamilton, J. G., M. H. Soley, and K. B. Eichorn. 1940. Deposition of radioactive iodine in human thyroid tissue. *Univ. Calif. Pub. Pharmacol.* 1:339-68.
- Hamilton, J. G., C. W. Asling, W. M. Garrison, and K. G. Scott. 1953. The accumulation, metabolism and biological effects of astatine in rats and monkeys. *Univ. Cal. Pub. Pharmacol.* 2:283-344.
- Hamilton, J. G., P. W. Durbin, C. W. Asling, and M. E. Johnson. 1955. Physiological and biochemical studies of astatine-211 (eka-iodine). In *Proceedings of the international conference on the peaceful uses of atomic energy* vol. 10, pp. 175-81. Held in Geneva, August 8-20, 1955. New York: United Nations. [Also UCRL-2901. Berkeley, Calif.: Univ. of Calif. Radiation Laboratory.]
- Harper, P. V., K. A. Lathrop, and P. Richards. 1964. Tc^{99m} as a radiocolloid. *J. Nucl. Med.* 5:382. [Abstract]
- Harper, P. V. et al. 1964. The use of ^{99m}Tc pertechnetate for thyroid, liver, and brain scanning. In *Proceedings of a symposium on medical uses of radioisotopes*. Vienna: International Atomic Energy Agency.
- Harper, P. V., W. D. Siemens, K. A. Lathrop, and H. Endlich. 1963. Production and use of iodine-125. *J. Nucl. Med.* 4:277-89.
- Hatanaka, H. et al. 1982. Boron-neutron capture therapy vs proton beam for malignant tumors—12 years' experience. Chapter 1 in *Modern neurosurgery*, vol. 1, pp. 122-26. New York: Springer-Verlag.
- Hayes, R. L. 1966. Radioisotopes of gallium. Chapter 33 in *Radioactive pharmaceuticals*, eds. G. A. Andrews, R. M. Kniseley, and H. N. Wagner, CONF-651111, pp. 603-18. Proceedings of a symposium held at Oak Ridge Institute of Nuclear Studies, November 1-4, 1965. Oak Ridge, Tenn.: U.S. Atomic Energy Commission.
- Henschke, U. K., A. G. James, and W. G. Myers. 1953. Radiogold seeds for cancer therapy. *Nucleonics* 11(5):46-48.
- Henschke, U. K., A. G. James, and W. G. Myers. 1954. Radiogold seeds in clinical radiation therapy. *Radiology* 63:390-99.
- Hershey, A. D., M. D. Kamen, J. W. Kennedy, and H. Gest. 1951. The mortality of bacteriophage containing assimilated radioactive phosphorus. *J. Gen. Physiol.* 34:305-19.
- Hertz, S., A. Roberts, and R. D. Evans. 1938. Radioactive iodine as an indicator in the study of thyroid physiology. *Proc. Soc. Exp. Biol. Med.* 38:510-13.
- Hine, G. J. and G. L. Brownell, eds. 1956. *Radiation dosimetry* [especially chapters 16 and 17]. New York-London: Academic Press.

- Hofer, K. G. and W. L. Hughes. 1971. Radiotoxicity of intranuclear tritium, 125 Iodine and 131 Iodine. *Radiat. Res.* 47:94-109.
- Holm, L-E., I. Dahlqvist, A. Israelsson, and G. Lundell. 1980. Malignant thyroid tumors after iodine-131 therapy. *N. Engl. J. Med.*, 303:188-91.
- Hughes, W. L., V. P. Bond, G. Brecher, E. P. Cronkite, R. B. Painter, H. Quastler, and F. G. Sherman. 1958. Cellular proliferation in the mouse as revealed by autoradiography with tritiated thymidine. *Proc. Nat. Acad. Sci. U.S.A.* 44:476-83.
- Hungate, F. P. and T. J. Mannell. 1952. Sulfur-35 as a mutagenic agent in neurospora. *Genetics* 37:709-19.
- Hursh, J. B. and N. L. Spoor. 1973. Data on man. Chapter 4 in *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh, pp. 197-239. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.
- ICRP. See International Commission on Radiological Protection.
- ICRU. See International Commission on Radiological Units and Measurements.
- International Commission on Radiological Protection. 1959. *Report of Committee II on permissible dose for internal radiation*. ICRP pub. 2. New York-London: Pergamon Press.
- International Commission on Radiological Protection. 1971. *Protection of the patient in radionuclide investigations*. Prepared in 1969, issued in 1971 as ICRP pub. 17. New York-Oxford: Pergamon Press.
- International Commission on Radiological Protection. 1979. Limits for intakes of radionuclides by workers. In *Annals of the ICRP*, ICRP pub. 30, pt. 1, vol. 2, pp. 3-4. New York.
- International Commission on Radiological Protection. 1982. Limits for intakes of radionuclides by workers. In *Annals of the ICRP*, ICRP pub. 30, Suppl. to pt. 3, vol. 7, pp. 1-3. New York.
- International Commission on Radiological Units and Measurements. 1962a. *Clinical dosimetry*. Report 10d, Handbook 87. Washington, D.C.: National Bureau of Standards.
- International Commission on Radiological Units and Measurements. 1962b. *Radiation quantities and units*. Report 10a, Handbook 84. Washington, D.C.: National Bureau of Standards.
- Johnson, H. A. 1970. Dose to the cell nucleus from tritiated thymidine. In *Medical radionuclides: Radiation dose and effects*, eds. R. J. Cloutier, C. L. Edwards, and W. S. Snyder, pp. 315-23. Proceedings of a symposium held at Oak Ridge Associated Universities, December 8-11, 1969. Washington, D.C.: U.S. Atomic Energy Commission and U.S. Public Health Service.
- Johnson, H. A. and E. P. Cronkite. 1959. The effect of tritiated thymidine on mouse spermatogonia. *Radiat. Res.* 11:825-31.
- Johnson, H. A. and E. P. Cronkite. 1967. The effect of tritiated thymidine on mortality and tumor incidence in mice. *Radiat. Res.* 30:488-96.
- Johnson, H. A., W. E. Haymaker, J. R. Rubini, T. M. Fliedner, V. P. Bond, E. P. Cronkite, and W. L. Hughes. 1960. A radioautographic study of human brain and glioblastoma multiforme after the in vivo uptake of tritiated thymidine. *Cancer* 13:636-42.
- Jones, H. B., C. J. Wrobel, and W. R. Lyons. 1944. A method of distributing beta-radiation to the reticulo-endothelial system and adjacent tissues. *J. Clin. Invest.* 23:783-88.
- Kieft, P. 1968. Induction of recessive lethals by ^3H -uridine and ^3H -thymidine in *Drosophila*. In *Biological effects of transmutation and decay of incorporated radioisotopes*, pp. 65-78. Proceedings of an IAEA symposium held October 9-13, 1967. Vienna: International Atomic Energy Agency.
- King, E. R., L. W. Brady, and H. C. Dudley. 1952. Therapeutic trials of radiogallium (Ga^{72}): A report of four cases. *Arch. Intern. Med.* 90:785-89. [Also King, E. R., M. W. Mason, M. B. Messinger, and H. C. Dudley, 1952. A preliminary report on the use of gallium 72 in clinical tracer studies. *Radiology* 59:844-48.]

- Korngold, L., G. L. Stahly, M. C. Dodd, and W. G. Myers. 1953. The comparative retention of antigen in the skin of immune and normal rabbits as determined with egg albumin labelled with radioactive iodine. *J. Immunol.* 70:345-51.
- Krisch, R. and M. Zelle. 1969. Biological effects of radioactive decay: The role of the transmutation effect. In *Advances in radiation biology*, eds. L. G. Augenstein, R. Mason, and M. Zelle, vol. 3, pp. 177-213. New York: Academic Press.
- Kyker, G. C. and J. J. Rafter. 1966. Colloidal properties of the lanthanides. Chapter 28 in *Radioactive pharmaceuticals*, eds. G. A. Andrews, R. M. Kniseley, and H. N. Wagner, CONF-651111, pp. 503-24. Proceedings of a symposium held at Oak Ridge Institute of Nuclear Studies, November 1-4, 1965. Oak Ridge, Tenn.: U.S. Atomic Energy Commission.
- Lambert, B. E. 1969. Cytological damage produced in the mouse testes by tritiated thymidine, tritiated water and x-rays. *Health Phys.* 17:547-57.
- Laughlin, J., R. Tilbury, and J. Dahl. 1971. The cyclotron: Source of short-lived radionuclides and positron emitters for medicine. Chapter 3 in *Recent advances in nuclear medicine*, ed. J. Lawrence, pp. 39-62. New York: Grune & Stratton.
- Lea, D. E. 1955. *Actions of radiations on living cells*, 2d. ed. Cambridge, England: Cambridge Univ. Press.
- Lee, W., R. P. Chiachierini, B. Schleien, and N. C. Telles. 1982. Thyroid tumors following ^{131}I or localized x irradiation to the thyroid and pituitary glands in rats. *Radiat. Res.* 92:307-19.
- Lipkin, M., B. Bell, and P. Sherlock. 1963. Cell proliferation kinetics in the gastrointestinal tract of man. I. Cell renewal in colon and rectum. *J. Clin. Invest.* 42:767-76.
- Lipkin, M., P. Sherlock, and B. Bell. 1963. Cell proliferation kinetics in the gastrointestinal tract of man. II. Cell renewal in stomach, ileum, colon, and rectum. *Gastroenterology* 45:721-29.
- Loevinger, R. 1970. Some remarks on the MIRD schema for absorbed-dose calculations for biologically-distributed radionuclides. In *Medical radionuclides: Radiation dose and effects*, eds. R. J. Cloutier, C. L. Edwards, and W. S. Snyder, CONF-691212. Proceedings of a symposium held at Oak Ridge Associated Universities, December 8-11, 1969. Springfield, Va.: National Technical Information Center.
- Loevinger, R. and M. Berman. 1968. A schema for absorbed-dose calculations for biologically-distributed radionuclides. MIRD pamphlet no. 1. *J. Nucl. Med. Suppl.* 1:7-14.
- Maldague, P., P. H. Que, and J. Maisin. 1962. Étude autoradiographique de l'incorporation de thymidine tritiée chez le rat. In *Tritium in the physical and biological sciences*, vol. 2, pp. 361-72. Vienna: International Atomic Energy Agency.
- Marinelli, L. D. 1942. Dosage determinations with radioactive isotopes. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* 47:210-16.
- Marinelli, L. D., E. H. Quimby, and G. J. Hine. 1948. Dosage determination with radioactive isotopes. II: Practical considerations in therapy and protection. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* 59:260-81.
- Marrian, D. H., B. Marshall, J. S. Mitchell, and I. Simon-Reuss. 1962. The treatment of cancer by a radioactive drug: Tritium-labelled tetra-sodium 2-methyl-1:4-naphthaquinol diphosphate. In *Tritium in the physical and biological sciences*, vol. 2, pp. 210-18. Vienna: International Atomic Energy Agency.
- Martin, R. F. and W. A. Haseltine. 1981. Range of radiochemical damage to DNA with decay of iodine-125. *Science* 213:896-98.
- Maxon, H. R., S. R. Thomas, E. L. Saenger, C. R. Buncher, and J. G. Kereiakes. 1977. Ionizing irradiation and the induction of clinically significant disease in the human thyroid gland. *Am. J. Med.* 63:967-78.
- Mayneord, W. V. 1950. Some applications of nuclear physics to medicine. *Br. J. Radiol. Suppl.* no. 2:153.
- Mewissen, D. J. and J. H. Rust. 1973. Tumor incidence in C57 black/6 mice treated with tritiated thymidine. In *Tritium*, eds. A. A. Moghissi and M. W. Carter, pp. 252-67. Phoenix and Las Vegas: Messenger Graphics.

- Morgan, K. Z. 1947 and 1980. Tolerance concentrations of radioactive substances. *J. Phys. Colloid Chem.* 51:984-1003. Reprinted as a landmark paper with comments by J. N. Stannard in *Health Phys.* 38:997-1014.
- Morgan, K. Z. and J. E. Turner, eds. 1973. *Principles of radiation protection: A textbook of health physics*. [Especially chapter 10, "Internal Exposure," by W. S. Snyder, pp. 301-65.] Huntington, N.Y.: Krieger Publishing.
- Mueller, G. and W. Myers. 1955. The 'Gammicon.' In *News in Engineering*, November 1955, pp. 3-6.
- Muller, J. H. 1965. Treatment of malignant disease with radiocolloids. Chapter 28 in *Blahd 1965*, pp. 705-37.
- Myers, W. G. 1965. Applications of radioiodine-125 in medicine and biology 1960-1964. In *Bericht über die 45. Tagung der Deutschen Röntgengesellschaft, in Gesellschaft für medizinische Radiologie, Strahlenbiologie und Nuklearmedizin e.V. Deutscher Roentgenkongress 1964* Georg Thieme, Stuttgart, Germany: Verlag.
- Myers, W. G. 1966a. Radioiodine-121. *J. Nucl. Med.* 7:390.
- Myers, W. G. 1966b. Radioisotopes of iodine. Chapter 12 in *Radioactive pharmaceuticals*, eds. G. A. Andrews, R. M. Kniseley, and H. N. Wagner, CONF-651111, pp. 217-43. Proceedings of a symposium held at Oak Ridge Institute of Nuclear Studies, November 1-4, 1965. Oak Ridge, Tenn.: U.S. Atomic Energy Commission.
- Myers, W. G. 1974a. Nuclear Medicine Pioneer Citation—1974. Hal Oscar Anger, D. Sc. (Hon). *J. Nucl. Med.* 15:471-73.
- Myers, W. G. 1974b. Radioiodine-123 for medical research and diagnosis. In *Recent advances in nuclear medicine*, ed. J. H. Lawrence, vol. 4, chapter 3, pp. 131-60. New York: Grune and Stratton.
- Myers, W. G. 1979. The Anger scintillation camera becomes of age. *J. Nucl. Med.* 20:565-67.
- Myers, W. G. 1981a. A taped personal interview at Columbus, Ohio, June 5, 1981.
- Myers, W. G. 1981b. SNM historian reflects on 40 years in nuclear medicine. *Soc. Nucl. Med. Newslines*, June 1981.
- Myers, W. G. 1984. Personal communication, December 7, 1984.
- Myers, W. G. and H. O. Anger. 1962. Radioiodine-123. *J. Nucl. Med.* 3:183. [Abstract]
- Myers, W. G. and W. W. Hunter, Jr. 1967. Radiocarbon-11 for scanning. *J. Nucl. Med.* 8:305. [Abstract]
- Myers, W. G. and H. C. Vanderleeden. 1960a. Radioiodine, I^{125} . *J. Nucl. Med.* 1:124-25. [Abstract]
- Myers, W. G. and J. C. Vanderleeden. 1960b. Radioiodine-125. *J. Nucl. Med.* 1:149-64.
- Myers, W. G. and H. N. Wagner, Jr. 1975. Nuclear medicine: How it began. In *Nuclear medicine: A hospital practice book*, ed. H. N. Wagner, Jr. H. P. Publishing Co., Inc.
- National Council on Radiation Protection and Measurements. 1959. *Maximum permissible body burden and maximum permissible concentration of radionuclides in air and water for occupational exposure*. Report no. 22 [originally issued as NBS Handbook 69]. Bethesda, Md.
- National Council on Radiation Protection and Measurements. 1979. *Tritium and other radionuclide labeled organic compounds incorporated in genetic material*. Report no. 63. Bethesda, Md.
- National Council on Radiation National Council on Radiation Protection and Measurements. 1985a. *General concepts for the dosimetry of internally deposited radionuclides*. Report no. 84. Bethesda, Md.
- National Council on Radiation Protection and Measurements. 1985b. *Induction of thyroid cancer by ionizing radiation*. Report no. 80. Bethesda, Md.
- National Council on Radiation Protection and Measurements. 1985c. *The experimental basis for adsorbed-dose calculations in medical uses of radionuclides*. Report no. 83. Bethesda, Md.
- NCRP: See National Council on Radiation Protection and Measurements.
- Okada, S. 1970. *Radiation biochemistry. I. Cells*. Especially chapters 3 and 7. Series by K. I. Altman, G. B. Gerber, and S. Okada. New York-London: Academic Press.

- Painter, R. B., F. Forro, Jr., and W. L. Hughes. 1958. Distribution of tritium-labelled thymidine in *Escherichia coli* during cell multiplication. *Nature* 181:328-29.
- Parker, H. M. 1950 and 1980. Tentative dose units for mixed radiations. *Radiology* 54:257-62. Reprinted as a landmark paper in *Health Phys.* 38:1021-24.
- Parker, H. M. 1981. Protection programs of the plutonium project. *Health Phys.* 41:571-76 [especially p. 572].
- Parrott, M., W. Garrison, P. Durbin, M. Johnson, H. Powell, and J. Hamilton. 1955. *The production and isolation of astatine-211 for biological studies*, UCRL-3065. Berkeley, Calif.: Univ. of Calif. Radiation Laboratory.
- Person, S., W. Snipes, and F. Krasin. 1976. Mutation production from tritium decay: A local effect for [^3H]2-adenosine and [^3H]6-thymidine decays. *Mutat. Res.* 34:327-32.
- Pochin, E. E. 1960. Leukaemia following radioiodine treatment of thyrotoxicosis. *Br. Med. J.* 2:1545-50.
- Prinzmetal, M., E. Cordey, R. J. Spritzler, and W. Flieg. 1949. Radiocardiology and its clinical applicability. *J. Am. Med. Assoc.* 139:617-22.
- Quastler, H. and F. G. Sherman. 1959. Cell population kinetics in the intestinal epithelium of the mouse. *Exp. Cell Res.* 17:420-38.
- Quimby, E. H. 1970. The development of radiation dosimetry in nuclear medicine. In *Medical radionuclides*, eds. R. J. Cloutier, C. L. Edwards, and W. S. Snyder, CONF-691212, pp. 7-31. Proceedings of a symposium held at Oak Ridge Associated Universities, December 8-11, 1969. Springfield, Va.: National Technical Information Service.
- Quimby, E. H. and S. Feitelberg. 1963. Dosage calculations for radioactive isotopes. In *Radioactive isotopes in medicine and biology*, 2d. ed., pp. 104-28. Philadelphia, Pa.: Lea and Febiger.
- Reactor Safety Study. 1975. *The Rasmussen Report*. WASH-1400. Washington, D.C.: U.S. Atomic Energy Commission.
- Richards, P. 1966a. Nuclide generators. Chapter 10 in *Radioactive pharmaceuticals*, eds. G. A. Andrews, R. M. Kniseley, and H. N. Wagner, CONF-651111, pp. 155-63. Proceedings of a symposium held at Oak Ridge Institute of Nuclear Studies, November 1-4, 1965. Oak Ridge, Tenn.: U.S. Atomic Energy Commission.
- Richards, P. 1966b. *The technetium-90m generator*. Chapter 10 in *Radioactive pharmaceuticals*, eds. G. A. Andrews, R. M. Kniseley, and H. N. Wagner, CONF-651111, pp. 323-34. Proceedings of a symposium held at Oak Ridge Institute of Nuclear Studies, November 1-4, 1965. Oak Ridge, Tenn.: U.S. Atomic Energy Commission.
- Robertson, J. S. 1981. Reconciliation of Marinelli and MIRD radiation absorbed dose formulas. *Health Phys.* 40:565-68.
- Robertson, J. S. and W. L. Hughes. 1959. Intracellular irradiation with tritium-labeled thymidine. In *Proceedings of the 1st national biophysics conference*, eds. H. Quastler and H. Morowitz, pp. 278-83. Held March 4-6, 1957. New Haven, Conn.: Yale Univ. Press.
- Rossi, H. H. 1967. Energy distribution in the absorption of radiation. In *Advances in biological and medical physics*, eds. J. H. Lawrence and J. W. Gofman, vol. 11, pp. 27-85. New York: Academic Press.
- Saenger, E. L. and J. G. Kereiakes. 1971. The safe tracer dose in medical investigation. In *Recent advances in nuclear medicine*, ed. J. Lawrence, vol. 3, pp. 139-65. New York: Grune & Stratton.
- Saenger, E. L., G. E. Thoma, and A. Tompkins. 1968. Incidence of leukemia following treatment of hyperthyroidism. Preliminary report of the cooperative thyrotoxicosis therapy follow-up study. *J. Am. Med. Assoc.* 205:855-62.
- Sayeg, J. and D. Preston. 1973. Dose reduction in thyroid uptake tests with I-125. In *Health physics in the healing arts*, DHEW pub. (FDA) 73-8029, pp. 605-11. Proceedings of the Health Physics Society topical symposium held in San Juan, Puerto Rico, December 1972. Washington, D.C.: U.S. Department of Health, Education and Welfare.
- Schultze, B. and W. Maurer. 1962. Comparative autoradiographic study of the RNA and protein metabolism within the various tissues and cells of the mouse with tritiated RNA precursors and labelled amino acids. In *Tritium in the physical and biological sciences*, vol. 2, pp. 229-36. Vienna: International Atomic Energy Agency.

- Seaborg, G. 1971. Remarks at the dedication of the Biomedical Cyclotron, Univ. of Calif. at Los Angeles, June 30, 1971. Washington, D.C.: U.S. Atomic Energy Commission.
- Seaborg, G. T. 1973. Medical uses: Americium-241; californium-252. Chapter 21 in *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh, pp. 929-40. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.
- Seaborg, G. T. and I. Perlman. 1948. Table of isotopes. *Rev. of Mod. Phys.* 20:585-667.
- Shellabarger, C. J., P. W. Durbin, M. W. Parrott, and J. G. Hamilton. 1954. Effects of thyroxine and KSCN on capacity of rat thyroid gland to accumulate astatine²¹¹. *Proc. Soc. Exp. Biol. Med.* 87:626-29.
- Shkurkin, C. J. and J. H. Lawrence. 1965. Treatment of blood diseases and malignancy with radioactive phosphorus in relation to other therapeutic agents. Chapter 27 in *Blahd 1965*, pp. 675-704.
- Smith, E. M. 1966. Internal radiation absorbed dose. Chapter 36 in *Radioactive pharmaceuticals*, eds. G. A. Andrews, R. M. Kniseley, and H. N. Wagner, CONF-651111, pp. 649-67. Proceedings of a symposium held at Oak Ridge Institute of Nuclear Studies, November 1-4, 1965. Oak Ridge, Tenn.: U.S. Atomic Energy Commission.
- Smith, E. M. 1968. Activities of the Medical Internal Radiation Dose Committee. Introduction to MIRD. *J. Nucl. Med. Suppl.* 1:5-6.
- Snyder, W. S. 1970. Estimation of absorbed fractions of energy from photon sources in body organs. In *Medical radionuclides: Radiation dose and effects*, eds. R. J. Cloutier, C. L. Edwards, and W. S. Snyder, CONF-691212, pp. 33-49. Proceedings of a symposium held at Oak Ridge Associated Universities, December 8-11, 1969. Springfield, Va.: National Technical Information Service.
- Snyder, W. S. 1973. Chapter 10 in Morgan and Turner 1973.
- Snyder, W. S. and M. R. Ford. 1965. A Monte-Carlo code for estimation of dose from gamma-ray sources. In *Health Physics Division annual report period ending July 31, 1965*, ORNL-3849, p. 193. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Snyder, W. S., M. R. Ford, and G. G. Warner. 1968. Effect of size, shape, composition, and density of body organs on the absorption of gamma rays from a uniform source in an organ. In *Health Physics Division annual report period ending July 31, 1968*, ORNL-4316, p. 274-76. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Snyder, W. S., M. R. Ford, and S. B. Watson. 1975. A computer program for estimating microcurie-days of a radionuclide in the organs of the human body. In *Health Physics Division annual report period ending June 30, 1975*, ORNL-5046, p. 225-29. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Snyder, W. S., M. R. Ford, J. W. Poston, and G. G. Warner. 1976. Estimates of photon dose to the gonads per microcurie-day as a function of the source organ and the age of the individual. In *Health Physics Division annual report period ending June 30, 1976*, ORNL-5171, p. 27-40. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Snyder, W. S., M. R. Ford, G. G. Warner, and H. L. Fisher, Jr. 1969. Estimates of absorbed fractions for monoenergetic photon sources uniformly distributed in various organs of a heterogeneous phantom. MIRD pamphlet no. 5. *J. Nucl. Med. Suppl.* 3:5-52.
- Snyder, W. S., M. R. Ford, G. G. Warner, and S. B. Watson. 1975a. A tabulation of dose equivalent per microcurie-day for source and target organs of an adult for various radionuclides. ORNL-5000, pt. 2. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Snyder, W. S., M. R. Ford, G. G. Warner, and S. B. Watson. 1975b. 'S', absorbed dose per unit accumulated activity for selected radionuclides and organs. MIRD pamphlet no. 11.
- Snyder, W. S., M. R. Ford, G. G. Warner, and S. B. Watson. 1975c. Tabulations of average dose equivalent due to radionuclides in body organs of an adult. In *Health Physics Division annual report period ending June 30, 1975*, ORNL-5046, p. 205-6. Oak Ridge, Tenn.: Oak Ridge National Laboratory.
- Spiers, F. W. 1968. *Radioisotopes in the human body: Physical and biological aspects*. [Part of the AIBS-AEC monograph series in radiation biology.] New York-London: Academic Press.

- Stent, G. S. and C. R. Fuerst. 1955. Inactivation of bacteriophages by decay of incorporated radioactive phosphorus. *J. Gen. Physiol.* 38:441-58.
- Strauss, L. 1962. *Men and decisions*, especially pp. 362-68. Garden City, N.Y.: Doubleday & Co., Inc.
- Sutherland, R. M. 1988. Personal communication, January 1988.
- Sweet, W. H. and M. Javid. 1952. The possible use of neutron-capturing isotopes such as boron¹⁰ in the treatment of neoplasms. I. Intracranial tumors. *J. Neurosurg.* 9:200-209.
- Taplin, G. V., D. E. Johnson, J. C. Kennedy, E. K. Dore, N. D. Poe, L. A. Swanson, and A. Greenberg. 1966. Aggregated albumin labeled with various radioisotopes. Chapter 29 in *Radioactive pharmaceuticals*, eds. G. A. Andrews, R. M. Kniseley, and H. N. Wagner, CONF-651111, pp. 525-52. Proceedings of a symposium held at Oak Ridge Institute of Nuclear Studies, November 1-4, 1965. Oak Ridge, Tenn.: U.S. Atomic Energy Commission.
- Taylor, J. H. 1962. Tritium and autoradiography in cell biology. In *Tritium in the physical and biological sciences*, vol. 2, pp. 221-28. Vienna: International Atomic Energy Agency.
- Taylor, J. H., P. S. Woods, and W. L. Hughes. 1957. The organization and duplication of chromosomes as revealed by autoradiographic studies using tritium-labeled thymidine. *Proc. Natl. Acad. Sci. U.S.A.* 43:122-28.
- Tomkins, E. 1970. Late effects of radioiodine therapy. In *Medical radionuclides: Radiation dose and effects*, eds. R. J. Cloutier, C. L. Edwards, and W. S. Snyder, CONF-691212, pp. 431-40. Proceedings of a symposium held at Oak Ridge Associated Universities, December 8-11, 1969. Springfield, Va.: National Technical Information Service.
- United Nations Committee on the Effects of Atomic Radiation. 1977. *Sources and effects of ionizing radiation*. Report to the General Assembly with annexes. New York: United Nations.
- UNSCEAR. See United Nations Committee on the Effects of Atomic Radiation.
- Vennart, J. 1969. Radiotoxicology of tritium and ¹⁴C compounds. *Health Phys.* 16:429-40.
- Verly, W. G. and G. Hunebelle. 1957. Preparation of ³H-thymidine. *Bull. Soc. Chim. Belg.* 66:640.
- Wagner, H. N., Jr. 1981. Hevesy: Nuclear medicine pioneer lecture [in honor of William G. Myers]. *J. Nucl. Med.* 22:573-76.
- Wagner, H. N. and H. Emmons. 1966. Characteristics of an ideal radiopharmaceutical. Chapter 1 in *Radioactive pharmaceuticals*, eds. G. A. Andrews, R. M. Kniseley, and H. N. Wagner, CONF-651111, pp. 1-32. Proceedings of a symposium held at Oak Ridge Institute of Nuclear Studies, November 1-4, 1965. Oak Ridge, Tenn.: U.S. Atomic Energy Commission.
- Wasserman, L. and J. Glass. 1968. The present status of therapy with radioactive isotopes. In *Progress in atomic medicine*, ed. J. H. Lawrence, vol. 2, pp. 113-67. New York: Grune & Stratton.
- Watts, R. and P. W. Durbin. 1956. *The distribution and acute effects of large doses of iodine-131 in the rat*. UCRL-3376. Berkeley, Calif.: Univ. of Calif. Radiation Laboratory.
- Wimber, N. 1964. Effects of intracellular irradiation with tritium. In *Advances in radiation biology*, eds. L. G. Augenstein, R. Mason, and H. Quastler, vol. 1, pp. 85-115. New York: Academic Press.
- Woodard, H. 1971. Personal letter.
- Woods, P. S. 1962. Autoradiographic studies of ribonucleic acid metabolism with tritium-labelled cytidine. In *Tritium in the physical and biological sciences*, vol. 2, pp. 335-46. Proceedings of a symposium held in Vienna, May 3-10, 1961. Vienna: International Atomic Energy Agency.
- Yagi, Y. and D. Pressman. 1964. Pair-labeled antitumor antibodies. *J. Nucl. Med.* 5:310-11.
- Yano, Y. and H. O. Anger. 1964. A gallium⁶⁸ positron cow for medical use. *J. Nucl. Med.* 5:484-88.
- Yokoro, K., A. Kunii, J. Furth, and P. W. Durbin. 1964. Tumor induction with astatine-211 in rats: Characterization of pituitary tumors. *Cancer Res.* 24:683-88.

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Chapter 21

Concluding Comments

I. Highlights

Many thousands of lives have been saved or made more comfortable by the uses of radioactive materials in medicine. This ranges from the early uses of the gamma rays from radium in encapsulated sources for the treatment of cancer and the insertion of radon seeds directly into areas suitable for such treatment, through the uses of radioisotopes of iodine, phosphorus, gold, and others for diagnosis or therapy, to the current enormous utilization of radioisotopes in nuclear medicine. (It is estimated that approximately one quarter of all hospital admissions now involve a nuclear medicine procedure at some stage.) This positive effect far exceeds the number of untoward effects of the uses of radiation and radioisotopes. If we add to this the tremendous advances in the understanding of biological processes at all levels, from molecular to the whole organism, made possible by the uses of radioactive materials as tracers, the balance becomes still more one-sided.^(a) Yet there has always been concern for proper control of the uses of radioactivity in industry and in medicine. This has ranged from rudimentary in the early days to stringent controls at present. While the accomplishments of nuclear medicine and of tracer chemistry have received ample attention and review over the years, the work and ideas of the cadre of scientists devoted largely to understanding all levels of effect and behavior of radionuclides from the apparently harmless to the obviously deleterious has not been systematically reviewed. The purpose of this book is such a review, with emphasis on work done in the United States.

Clearly we have learned much, but clearly there is much left to be learned. In this first section of the concluding chapter we will list some of the highlights of what we have learned. In a later section, we will list some of the problems for the future.

(a) See, for example, Hearings on Applications of Radioisotopes and Radiation in the Life Sciences (U.S. Congress 1961). This early version required four days. Now thousands of experiments are based on radioisotope techniques.

A. What Have We Learned About Effects?

It is clear that *qualitatively* the effects of ionizing radiation from deposited radionuclides are comparable to those from external radiation sources. It is equally clear that there are quantitative differences. Many of these reside in the fact that radioisotopes are seldom distributed uniformly in body tissues. There are nearly always tissues or organs with concentrations well above the average. More effect is seen with these to a degree dependent on the energy and range of the emitted radiations as well as concentration. In many cases, effects, especially long-term effects, may be almost entirely confined to a single tissue or organ, such as bone or thyroid. These properties underlie most of the attempts to use radionuclides in therapy. They also lead to instances where effects appear in a system that never would have shown itself under most conditions of external radiation.

There are large differences in the effectiveness of different deposited radionuclides, even in the same tissue. These go well beyond any differences in absorbed dose, even beyond differences due to different linear-energy transfer (LET) rates noted with external radiation. They reside in differences in the microlocalization of the atoms with reference to the most sensitive or target cells. The phenomenon was earliest and best illustrated by differences between those bone-seeking elements that exchange for calcium (e.g., radium and strontium) and thus distribute eventually throughout the volume of bone and those that deposit primarily on surfaces within bone (e.g., plutonium, the transplutonic elements, many of the rare-earth-type elements). Because of the practical importance of these phenomena for standard-setting, and their inherent scientific interest, many extensive experiments were performed. Some of these are among the longest biomedical experiments ever brought to fruition because of the very long latent period involved in the production of the effects of most concern.

There are persistent differences among animal species in the mix and quantitative aspects of both short- and long-term effects. These differences stimulated the introduction of new species and new strains and attempts to explain the phenomena noted. In some cases, the phenomena have been explainable, in other cases not. Sometimes new species or strains have shown more consistent behavior than was earlier revealed. The phenomena sometimes support the statement that "the proper subject for the study of man is man" (Evans 1983), and emphasize the need to extract all possible information from the ongoing studies on man. Nevertheless, there is much needed information that can be obtained only by experiments that could not possibly be done with man as the subject. Thus, best-guess extrapolations to man have been consistently needed and have required much effort.

The new dimensions brought upon the biomedical world by the production of the fission products in large quantity and the *de novo* presence of plutonium and related actinides led to advances in our knowledge that would never have occurred otherwise, at least not in so short a time frame. The concentrated attacks on these made during the war years under the aegis of the Manhattan Engineer District (MED) have stood the test of time and formed the basis for much additional work.

A similar large effort surrounded natural uranium, although it was not quite a "new dimension." Chemical toxicity to the kidney, the most likely acute effect, vies with potential long-term radiation effects as a basis for exposure standards to uranium.

The primary expected route of entry into the body of radionuclides released in the workplace is inhalation. A large amount of experimental work has concentrated on the inhalation route. Indeed, one major installation has been devoted almost entirely to inhalation experiments. It has turned out that deposits of insoluble forms of radionuclides in the lungs can be a potent source of lung cancer, sometimes exceeding the potential for bone cancer. In addition, much has been learned about respiratory physiology and pathology in the course of this work.

The role of radon daughter products in the production of lung cancer in uranium and other hard-rock miners has been proven beyond doubt. The saga of the miners covers by far the longest period of investigation depicted in this book. The results of studies of animals and of man indicate a possible species difference in the site of origin of the lung cancer and thus in the mechanism. The role of adjuvants has been especially thoroughly investigated in this work, but the answers are equivocal. Natural radon in homes is an important new dimension.

Throughout the work on inhalation effects, it has been necessary to construct reliable systems for the controlled production of radioactive aerosols. These techniques and installations have been unique and led the way for all of inhalation toxicology.

The potential for effects of radionuclides released to the environment from nuclear installations was one basis for development of an entirely new field, radioecology.

The new dimension of fallout from nuclear weapons testing led to much work on the possible effects of low doses of deposited radionuclides in humans, animals, and in ecosystems, as well as on the movement of radionuclides in environmental media.

Dosage calculations associated with effects of deposited radionuclides follow two major systems, the classical system usually attributed to Marinelli, Quimby, and Hine and a system developed by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine. The basic principles of both systems are given in the text, but many of the complexities have been omitted. This was done, in part, because the dosimetric systems have, in this author's view, become complex far beyond the precision needed for biomedical work. Nevertheless, even with the most complex formulations, it is not possible to answer *simply* whether or not a given absorbed dose of radiation from a deposited radionuclide has the same effect, quantitatively, as the same absorbed dose from an external source. There are instances where there appears to be a significant difference. Attempts are still being made to attribute some of these to a chemical effect of the element concerned, but they have not been notably successful, except for natural uranium.

Very low-energy beta emitters may produce more or less specific effects within cells in which they are localized. Radioisotopes that produce Auger electrons likewise appear to have unique properties vis-à-vis the effects they produce.

On the whole, radionuclides do not deposit selectively in gonadal tissue and unique mutational events from this source are not common. The risk from genetic effects thus is, in general, comparable to the same dose from an external source. However, the amount of work done in this field is small relative to the needs.

The possibility of a transmutation effect (when a radionuclide that is incorporated in a vital macromolecule decays and thus becomes a new element) has

received much attention. On balance, it appears that bona fide transmutation effects occur only under rather special circumstances. They contribute little to the overall effects of deposited radionuclides.

The dose-response curves for the effects of deposited radionuclides are frequently complex. Their shape is seldom simple linearity but rather a linear component followed by a dose-squared or other components with indications of other shapes, including ones consistent with the idea of a "practical threshold." This is discussed especially in connection with the bone-seeking radionuclides. It appears that the assumption of linearity for purposes of standard-setting must be considered a rather gross simplification in many cases.

Dose fractionation experiments did not provide answers identical to those expected from experience with external sources. While some experiments with beta and beta-gamma emitters indicated lesser effects with protracted or fractionated doses, others, particularly with alpha emitters, appeared to show greater effectiveness of protracted doses. Since the radionuclide is sometimes present for long periods, the situation is rather different from that with an external source that can be turned off completely.

Much effort around the "hot particle" problem failed to demonstrate, in general, any greater or any special effect of exposures to these intense sources.

During World War II, and in the immediate postwar years, interests centered on the acute effects of moderate to high doses of radiation from either external or internal sources, and this occurred despite the accumulating information on long-term effects in the radium dial painters and patients (chapter 1). By contrast, in the post-World-War-II era, much emphasis was placed upon formal study of the longer-term effects of radiation. Both external sources and deposited radionuclides were involved. Beginning with longer observation periods on animals receiving moderate, even high doses, the work extended gradually to lower and lower administered doses and body burdens. In the late 1940s and early 1950s, rodent colonies contributed most of the information. Later the large life-span beagle studies confirmed and expanded the picture (chapters 8 and 13). Because of the interest in using the relative carcinogenic potential of several bone-seeking elements for development of exposure standards using radium as the bench mark (chapter 16), much emphasis was placed on plutonium, americium, other actinides, and strontium. There were also long-term experiments on radioiodine, particularly involving rodents and miniature swine (chapter 8).

Much was learned about the carcinogenic potential and general effects of these and related elements on many physiological systems. These are detailed at appropriate places throughout the text, and are summarized in the paragraphs above.

We still need more information, especially at very low doses, but in toto we have gained, by orders of magnitude, in our comprehension of the long-term effects of deposited radionuclides. In fact, more is probably known about these than about the majority of chemically toxic entities in the work place or the environment.

B. Metabolism (Pharmacokinetics)

It was necessary to determine the behavior in various living systems of any and all radioactive materials under study. While in general their behavior might be predictable from the chemistry of the element involved, the quantitative aspects were frequently not well enough established and had to be fleshed

out by work with radioisotopes. There were some unexpected differences from predictions.

As expected, chemical form played an important role in lung or gut uptake, as well as in subsequent distribution to tissues. For inhalation exposures, the particle size and its distribution were added factors and of considerable importance. It soon became apparent that many radionuclides formed complexes of varying degrees of stability with ligands in blood and/or tissues. In the earlier studies, complexing was especially well worked out for uranium. Also, complexes and methods for induction of complexing undergirded much of the work aimed at therapeutic removal of deposited radionuclides.

It was also apparent that colloidal states existed in many instances; in both injection solutions and in vivo. This led to uptake by, and the usual reactions of, the reticuloendothelial system (RES) to particles of colloidal size. Deposit and retention in tissues such as liver, spleen, and bone marrow frequently followed. By contrast, the same substances entering via absorption from the gastrointestinal tract or, to a lesser degree from the lung, were less likely to be in colloidal form and thus go to the RES in lesser quantity. Differences in distribution and excretion followed these different routes of entry.

The retention of radionuclides in tissues was subject to intensive kinetic analysis. This was needed partly to serve the needs of dosage calculations and partly for its intrinsic interest. Normal physiological concepts predict first-order kinetics of loss from each of one or more compartments. Many retention data could be fitted by exponential functions of time, most frequently by two or several, rather than by one exponential, indicating more than one compartment of retention. Frequently, however, particularly for long-lived, long-retained radionuclides, the data were fitted best by a power function of time. This may represent only the summation of many exponentials, but has impressed many investigators enough to be advocated as a formulation for practical use.

Each group of radionuclides has, of course, its own pharmacokinetic pattern, modified by the presence or absence and nature of complexers. Unexpected was the finding that different isotopes of the same element could exhibit different metabolic patterns (e.g., ^{238}Pu differs from ^{239}Pu , the iodine isotopes differ from each other). Differences in specific activity may underlie some of these phenomena with, for example, higher-specific-activity materials causing radiation-based destruction of complexes or of imbibing cells. The net result is a need for actual study of each isotope of interest. Projections on a generic basis are not enough. A start has been made on such experiments, but only a start.

The behavior of inhaled radionuclides was likewise not accurately predictable. There appears to be no substitute for an actual inhalation exposure experiment. Even intratracheal instillation is not the same.

Judicious tracer-level experiments in humans indicated reasonably satisfactory agreement between the metabolic data obtained from animals and those found in man. Some of the noted differences can be explained on the basis of anatomy (e.g., the relative amounts of cortical and trabecular bone) and thus reconciled. There were occasionally wide differences in excretion rates among animal species and between some animal species and man that require consideration for bioassay procedures. Only a few of these differences have been explained.

Experience around nuclear sites and with fallout from weapons tests provided much information on the movement of radionuclides in the biosphere. Conversely, the presence of radionuclides helped to describe major movements in

components of the environment, such as the atmosphere and the hydrosphere. The fact that many organisms can act as sinks for radioactivity and thus contribute to gradual increases in tissue concentrations as one progresses up the trophic chain was amply demonstrated. Differences in the movement of radionuclides in different environments and in different organisms led to the concept of critical pathway and its corollary, the critical population, in the setting of population exposure standards. Now the accumulated information supports extensive computer models for environmental transfer. Correlates of the information on environmental transfer extended to the development of environmental impact statements and have been important in undertakings such as Project Plowshare.

Information gained from some of the environmental experiments led to cancellation of planned projects.

Some broad features of many of the ocean currents and of atmospheric circulation patterns, including the jet stream, have been developed, in part, using data for radioisotope transfer developed from the measurements of fallout from weapons tests.

Biological entities play an important role in some of the environmental transfer systems, a relatively minor role in others.

C. Applications

In addition to the intrinsic interest in finding out about the metabolism and effects of both natural and manmade radioisotopes, there were many practical needs served by the research efforts described in this book.

A consistent focus of the investigations has always been the development of realistic standards for limiting intake of radionuclides. The research data have been enormously useful for this, indeed essential. The applications have been in two forms:

1. *Direct use of observed effects as a function of dose or body burden.* The classic example is the standard for ^{226}Ra that was developed entirely by the finding of levels in humans that were or were not associated with observable biological effects. This standard, developed in 1940 and published in 1941, has remained valid ever since, confirmed and strengthened by additional information. An exposure standard for radon was developed at the same time based upon measurements, industrial hygiene style, of air concentrations in the work environment, correlated with evidence of effects in humans. A third example is the standard for uranium, which was derived largely from data obtained in animal experiments since effects in man were marginal or not observed.

Direct derivation in humans of a standard for plutonium was not possible, thankfully, for the same reason, lack of significant numbers of clearly affected individuals. However, the standard for it was based upon the radium standard and was thus quasi-direct. To do this, the relative effectiveness of plutonium and radium was determined in several large animal experiments and the ratio of allowable body burdens equated to the ratio of effectiveness. As new data accumulate, we can expect further attempts to calculate risk to humans for other radionuclides directly from the data on effects:

2. *The indirect or computational approach.* When it was decided to set standards for the many hundreds of radionuclides developed in the years of the MED, a different approach was needed, since sufficient data for a direct approach existed for only a few. To accomplish this, the limits were set by

computation of the radiation dose rate to the target organ (critical organ) or whole body, and intake was limited so that the delivered dose would never exceed that allowed the same organ or tissue from external radiation sources such as x or gamma rays. This required knowledge of gastrointestinal-tract absorption, behavior in the respiratory tract, distribution to the various tissues and organs, retention therein, and the kinetics of excretion. All of the research data gathered on humans and animals concerning pharmacokinetics (metabolism) were screened for this purpose. Best estimates were made for the parameters needed for the computations. In some cases, the amount of information was insufficient, and decisions had to be made by reference to analogues. Also, because the quantities involved with many radionuclides were exceedingly small (by weight), it was desirable to know the amounts of many trace elements already present in the tissues of humans. Thus, the "pool" size into which the radioactive isotope would be diluted could be determined. A special project was operated to determine these trace element quantities in humans.

The computational approach has now reached enormous proportions. Beginning with the 1959 reports of the U.S. National Council on Radiation Protection and Measurements (NCRP) and of the International Commission on Radiological Protection (ICRP) and the subsequent compilations by the Atomic Energy Commission (AEC) and the Nuclear Regulatory Commission (NRC) into Federal Regulations and many other intermediate stages, we see a culmination (for the present at least) in the enormous volumes from the ICRP published in the recent past (cited in chapter 16). These give physical and biological data and the calculated annual limits on intake and derived air concentrations for over seven hundred radionuclides. The bulk of the data used is on file, and the computations were made at the Internal Dosimetry facility of Oak Ridge National Laboratory. Revisions and expansions to population exposures are now in preparation. These and all other documents, past and future, depend entirely upon the research data generated in the projects described in this book.

The research data have also been brought to bear on the validation of standards already extant. Several epidemiologic investigations are described that have particular significance for this purpose. As new epidemiologic work grows and current projects come to completion, we can expect a considerable expansion in this validation process.

The research data have been used for developing specialized models such as those for behavior of radionuclides in the respiratory tract and in the gastrointestinal tract, the behavior of alkaline earth elements in bone, and others.

An additional need was to define average anatomical, physiological, and biochemical parameters of humans for use in computations or model making. As a result, collaborative work between investigators in the radionuclide field and conventional anatomists, physiologists, and biochemists led to development of a "standard man," now called "Reference Man."

The fields we now know as nuclear medicine and as tracer chemistry had a common origin among investigators interested in the applications and use of radionuclides. While each now has its own identity, the research described in this book contributed significantly to each and vice versa. This is reviewed primarily in chapters 5 and 20.

The attempts to develop therapeutic means for removal of deposited radionuclides rested squarely upon applications of the knowledge about their behavior already gained. Conversely, the special studies of therapy added new information concerning the behavior of radionuclides in living organisms. This

included the finding that fixation could occur quite rapidly, and early institution of therapy was frequently essential.

Many applications of the research described in this book are more or less indirect, indeed, symbiotic. Among these would be the developments in therapy with radioisotopes and diagnostic procedures used in nuclear medicine (chapter 20); development and use of environmental transfer functions; the basic inputs for environmental impact statements and the like (chapters 11 and 15).

An example of an even more indirect application can be seen in the development of new strains of salmon and trout through the University of Washington program. This development was technically almost separate from the radiobiology program and of much longer standing, but it was clearly advanced by the presence of the financial support and activities that spilled over from it. Hines (1976), in a charming and comprehensive book entitled *Fish of Rare Breeding—Salmon and Trout of the Donaldson Strains*, describes the fisheries program that began in the 1930s and is still active. It was primarily a genetic selection program, but eventually became a "farm" operation. It is safe to say that productivity of Pacific species was notably enhanced, and also strains developed that have played a major role in the repopulation of some, if not all, of the Great Lakes and other bodies of fresh water. To a degree, the radiation program piggybacked, intellectually at least, on this long-standing effort. Yet, there was clearly more work possible because of the program built around understanding possible effects of effluents from the Hanford reactors.

A picture of Dr. Donaldson with one of his "pets" is shown as figure 21.1.



FIGURE 21.1. Dr. Lauren Donaldson with one of his "pets" at the University of Washington. (From Hines 1976.)

II. Correlates to Mechanisms

A. The Setting

On several occasions in the description of the research efforts, it was noted that the investigators took every reasonable opportunity to seek mechanistic explanations for the phenomena observed. In the early years, biomedical science was not far enough advanced for any review of the mechanisms proposed to have

current meaning. Therefore, these have been omitted for the most part. During the years of the MED, the generation of empirical data on behavior and effects had to take precedence. Mechanisms were guessed at and some work done, but serious investigations into them had to be postponed. After the pressures of the war years were over, more time and resources could be and were devoted to seeking explanations for the phenomena observed. Some of these have been noted along with the descriptions of the findings; for example, the basis for discrimination factors between pairs of isotopes (chapter 13), the likely explanations for some of the transfer and concentration factors in the environment (chapter 15). In other cases, independent studies were mounted to go further into mechanisms. These are not reviewed in any detail in the individual chapters. A few are summarized very briefly herein. In still other cases, it can be said that a whole new field grew from the initial forays into mechanisms. An example of this will be given in this section.

In a sense, this section might be labeled "spin-offs to basic science." However, this appellation implies a qualitative difference in objectives that is not appropriate to the field of this review. If we define "basic science" as science done with absolutely no thought of the reasons for doing it, then none of the work we have been or are discussing could be called basic science. All of it had fairly specific objectives. A more suitable discrimination is between mechanistic and descriptive considerations.

B. Cellular-Level Correlates to Mechanisms

There are many possible examples. We will emphasize only a few.^(a)

1. Uranium and Cell Surface Enzymes

In chapter 2, we noted that the attempts in the work at Rochester to understand the mechanisms of uranium poisoning uncovered the presence of enzymatic poisoning in and on the cell surface. This essentially developed into the field of membrane biophysics as we know it today. The principal investigator involved was Dr. Aser Rothstein, now Director of the Research Institute at the Hospital for Sick Children in Toronto, Canada. Let us review the development in Dr. Rothstein's own words (Rothstein 1983), somewhat more circumspect than the broad generalization made above:

If you remember, after the war-pressure was lifted, I started to explore the effect of uranyl ion on sugar transport in yeast, stimulated by my Ph.D. thesis on membrane function in that cell, and by the known effect of uranyl on sugar reabsorption in the kidney. It turned out that uranyl was an excellent probe for transport systems because it didn't penetrate and because it interacted chemically with finite, chemically definable, functionally important populations of binding sites on the surface of the cell. It was probably the first use of a chemical impermeant probe for quantitative assessment of functional cell surface ligands. It certainly was an early demonstration of functional activities of the cell membrane. It led me later, in connection with studies on mercury toxicity, into the use of mercurials and other sulfhydryl agents to probe the role of sulfhydryl groups, and therefore proteins, in transport activities. My present work on anion transport proteins is in the line of direct descent from the uranium and mercury studies. We developed a series of affinity probes relating to inhibitors of anion transport, which were used to identify the

(a) Correlates to bone and to carcinogenesis are discussed separately.

anion transport protein in 1974. This was probably the first transport protein so identified, although the enzyme Na-K-ATPase had been earlier identified as playing a role in Na^+/K^+ transport. As a consequence of the identification of the anion transport protein, it has become an important model system for understanding protein-mediated transport and the structure of transport proteins. Several hundred papers have been published in the last ten years, a fair proportion from my laboratory. . . . So in summary, there is an evolutionary line from the uranium studies to the anion transport protein.
(Rothstein 1983)

The cell membrane continues to gain in importance in many phenomena, including immunological reactions. While many other fields are now contributing to it, this provides an excellent example of how a career and a field of investigation got their start in curiosity about the mechanism of action of one of the prime elements discussed in this book.

2. Tritium and the Dynamic State of Body Constituents

In discussing the behavior of tritium in chapter 10, and its incorporation into nucleic acid precursors in chapter 20, various cellular mechanistic correlates were described. Of additional interest is a series of investigations with tritium carried out by R. C. Thompson and J. E. Ballou at Hanford in the early postwar years. At that time, biochemists were greatly impressed by the new evidence for mobility of various moieties in body constituents that were previously thought to be more or less static. This had led to much discussion of the "dynamic state of body constituents," based largely upon evidence gained from tracer experiments.

As part of the researches at Hanford into the biological behavior and hazards of tritium, Thompson and Ballou noted that the tritium did not pass through as if it were wholly contained in the body water. This was developed in studies involving the mouse (Thompson 1952), the rat (Thompson 1953), individual tissues from the rat (Thompson and Ballou 1954), and concluded that many body constituents, in the rat at least, were not in a dynamic state at all (Thompson and Ballou 1956).

The fact that collagen seemed to be relatively nondynamic had already been appreciated. This work with tritium indicated that nearly every tissue, but blood, had components to which tritium was bound for very appreciable periods. Also, there were many entities in which this relatively long-term binding could occur. It is not a large portion of the total tritium. Much of it does, indeed, exchange rapidly. However, the presence of the phenomenon led to modification of the concepts regarding the dynamic state of body constituents. It also had significance for the determination of radiation dose, not only for tritium, but for many radionuclides, since the presence of long-term binding has been found for many.

3. Cellular-Level Dosimetry

Dosimetry for deposited radionuclides at the tissue or whole organism level is admittedly complex (chapters 9 and 20). Most dosimetry at the cellular level has been based upon phenomena observed with external radiation sources. Yet, there have been contributions from attempts to understand doses to cells and their components, particularly for the high-LET alpha particles of deposited radium, plutonium, and other important radioactive elements. The hot particle

controversy (chapter 9) did much to stimulate further investigation and calculation. Thus, Barendsen (1964) looked specifically at the proliferative capacity of cells in tissue culture treated with alpha particles and expounded on the mechanisms of action of the different ionizing radiations (Barendsen 1967). Other examples are the estimation of cell traversals by alpha-particle tracks from plutonium in the lung presented in the NCRP "Hot Particle" report (NCRP 1975), the theoretical considerations in the same report, the replacement of absorbed dose by the concept of "specific energy" in a microscopic region (Roesch 1977; Rossi 1967), and related theoretical treatments. A recent review of the whole problem of mean dose versus local dose in the respiratory tract was presented by Cross and Bair (1984).

Recently, Dr. John Little, at Harvard, has extended to internal emitters his technique for studying mutagenesis and transformation in mammalian cells. Among other things, he has demonstrated the extreme effectiveness at the cellular level of elements that emit Auger electrons. Earlier work with these is discussed briefly in chapter 10.

4. Other Cellular Aspects

The possible role of cells of various origins, especially cells in the lymphocytic line, in the genesis of radiation effects has been of great interest.^(a) Much of the work involves external radiation. A good source of summary information comes from the proceedings of a Hanford biology symposium entitled *Radiation and the Lymphatic System* (Ballou 1976). Several of the papers pertain to deposited radionuclides. There are two modes of action of special pertinence to work with these: (1) effects of the radiation from the radioisotope on cells of the lymphocytic line, and (2) the role of various cellular reactions on the distribution and excretion and effects of the radionuclide. The production of lymphocytopenia is a classic result of exposure to external sources of ionizing radiation. It has likewise been characteristic of deposited radionuclides. Much effort has gone into determining mechanisms by varying dose patterns, the nuclides, or both.

Some of the work from the Lovelace Inhalation Toxicology Laboratory is illustrative. Jones et al. (1976) gave graded lung burdens of several beta-gamma-emitting isotopes in fused clay to dogs and studied the effects on peripheral lymphocytes. While the effects were largely as expected in relation to lung burden, dose rate, etc., two of the isotopes produced a prolonged lymphopenia that persisted through two and one-half years after the exposure. The other two did not. This was notable because the lymphocytes were not receiving any prolonged radiation dose except from the deposits in tracheobronchial lymph nodes. Could the occasional passage of circulating lymphocytes through these nodes account for such a persistent depression? This is not a unique observation. It will be recalled that animals in the radon experiments at Rochester showed incomplete recovery of red cell count for a long period after exposure. Another approach was to test the ability of lymphocytes to respond to stimuli such as plant mitogen (Benjamin et al. 1976).

Also, work from Battelle over many years examined the possible mechanisms of induction of lymphocytopenia with plutonium (Ragan et al. 1976, work cited therein and in chapter 9).

(a) Upton (1976) says: "Of all the tissues of the body, the lymphatic system, perhaps as much as any other, symbolizes our reactivity to environmental stimuli."

Chromosome aberrations have been noted in lymphocytes from animals and humans receiving moderately low doses of external radiation. It was thought that the persistent deposits of radionuclides seen in lung, bone, liver, and so forth, might be much more effective in this regard than a single dose of external radiation. Results with both animal and human populations have not been consistent. In some cases, the results encouraged use of chromosome aberrations in lymphocytes as a biological indicator of early cellular change. In other cases, the promise seemed empty. Several of the animal experiments were negative at calculated doses that produced positive results in humans.^(a) Brooks et al. (1976) speculated on these differences. Is the lymphocytic line less sensitive in the animal models used? Are there other chromosome-breaking agents present in some cases and not in others? On the whole, the work with internal emitters, including work in humans with radium (Heogerman, Cummins, and Bronec 1976) does not indicate that blood lymphocytes will be a sensitive indicator of early biological damage.

Turning from the effects of the radionuclides on cells to the effects of cells on the deposition, clearance, and binding of radionuclides or in moderating their effects, we enter another arena. We have already seen that phagocytosis plays an important role in the transport of radionuclides. This may be best portrayed in the action of pulmonary macrophages (see chapter 9). More subtle are the important parts played by changes in immune reactions associated with the cells that interact with radionuclides or encounter biological changes already initiated by them. An interesting example is found in some of the work from Battelle (Frazier, Lund, and Busch 1976). The picture is shown in the abstract of this paper quoted below:

Cell cultures have been prepared from lung and bone tumors arising in beagle dogs following exposure to inhaled plutonium. Evaluation of the cultured cells by commonly applied criteria (i.e., cell morphology, lack of contact inhibitory mechanisms, cloning efficiency, growth in soft agar, and tumor production *in vivo*) indicated that tumor cells were being grown in culture.

Blood leukocytes and peripheral lymphocytes from beagle dogs were tested for cytotoxic effects against several cell cultures. Lymphocytes from normal dogs or dogs with unrelated tumors would not kill the bone tumor cells unless monocytes (macrophage) were present, in which case the leukocyte preparation was capable of mounting *de novo* cytotoxic immune reactions after 3 to 5 days in culture. In contrast, the dogs with plutonium-induced bone tumors had circulating lymphocytes that appeared to have undergone presensitization to bone-tumor-distinctive antigens *in vivo*. Consequently these lymphocytes interacted with cultured cells promptly after encounter *in vitro*.
(Frazier, Lund, and Busch 1976)

Many other examples could be given.

Among the conclusions of the Hanford meeting on radiation and the lymphatics were some complexities and dilemmas (Stannard 1976). For example, cell morphology does not always indicate function. Cells that look alike may serve different functions depending upon their biochemical and immunological history. Conversely, some cells that appear different morphologically may serve similar functions. Lymphocytes are not all alike. It depends on where they have been, what influences they have been subjected to. We can, at present, only guess at many of the interactions of importance.

(a) For example, experiments with radium, plutonium, Thorotrast, iodine.

C. Bone

Undoubtedly the research efforts with deposited radionuclides have contributed more to understanding of the mechanisms of events in bone than any other single area. This is partly because so many radionuclides deposit preferentially in bone; partly because the saga of the radium dial painters and patients and the problems of fallout focused attention on bone; partly because data pertaining to mechanisms were almost automatically produced in the studies of the behavior of bone-seeking radionuclides. There is a very large literature, much of it already considered in earlier chapters. Some, which focused primarily on mechanisms, will be reviewed, in part, here.

1. Cellular and Submicroscopic Events in Bone

The field had a good start before the advent of the atomic age. The fact that the crystal structure of bone closely resembled that of the mineral calcium hydroxyapatite was established by x-ray diffraction measurements in the late 1920s and early 1930s. But it took the investigations with radioisotopes to show that bone was much more than a static supporting structure, even in its mineral phases, and that resorption and remodeling were constantly under way. This was why administered isotopes were found to move about in bone and to be gradually buried in the processes of bone growth. It was in 1935 that Hevesy, using ^{32}P , found that there was rapid exchange of phosphate between plasma and bone (see McLean and Budy 1964). The phenomena of exchange in both bone mineral and in the organic matrix have occupied attention ever since.

The enormous effort with radiostrontium proved the fact that it, like radium, entered bone by exchange for calcium and that there was a strontium hydroxyapatite (Engström et al. 1957). The details of bone remodeling were worked out with elements like radiostrontium, radiocalcium, and radium. Autoradiography with both beta emitters and alpha emitters helped to elucidate the role of the several entities such as osteoclasts and osteoblasts, osteocytes and cartilage in the processes of bone growth.

As soon as the dynamic state of bone was established, it was of interest to see if the mechanisms of action of parathyroid hormone and of vitamin D could be worked out at the cellular or molecular level. McLean and Budy (1964) review much of the evidence, including the idea that there is a second hormone, calcitonin, that takes part along with parathyroid hormone in the regulation of calcium metabolism. Of special interest is a unifying concept developed by W. F. and M. W. Neuman (1958) that all aspects of the action of parathyroid hormone can be explained in terms of its ability to enhance the transport of inorganic phosphate into cells.

This latter work represents another direct extension to mechanisms from wartime programmatic research. Neuman and his colleagues spearheaded much of the biochemical work on uranium at the Rochester Project (chapter 2). This began a lifelong interest in physical and biochemical problems of bone. The work went far beyond the action of modifying factors into basic mechanisms. Let us quote from the summary of the chapter on skeletal dynamics in the Neuman and Neuman monograph:

The three ion-transfer mechanisms characteristic of hydroxy apatite *in vitro*—(a) diffusion in the hydration shell, (b) ion exchange at the crystal surface, and (c) intracrystalline exchange—all occur in the animal, but they are modified under the influence of physiological conditions: new growth, vascularity, remodeling and

maturation of bone, and the regulation of absorption and excretion of minerals in the intestine and kidney. At the histological level the age of the bone structure is the primary determination of its reactivity. The newly forming osteone very quickly mineralizes to nearly 90 per cent of its maximal mineral content, displacing the water of hydration in the process and thus inhibiting the penetration of ions. At full mineralization, physicochemical reactions grind to a virtual halt. Such old, unreactive bone elements compromise the metabolically inert, unavailable skeleton which in the adult animal is about two-thirds of the total.

The continuing maturation of bone imparts an irreversibility to the exchange of ions, and, while injected crystal-seeking radioisotopes show a histological distribution reflecting the patterns of growth and remodeling, the complexity of the overlapping rates of exchange, new growth, remodeling, and maturation has frustrated attempts to analyze these processes quantitatively. At present, it can only be said that the exchange process predominates in short-term (24-hour) observations and that new growth, remodeling, and maturation dominate longer periods of observation. The maturation process is also responsible for the permanence of skeletally deposited body burdens of radioisotopes and the failure of therapeutic procedures to mobilize them.

There is, however, a continuous supply of young, reactive bone made available by growth and Haversian remodeling. This constitutes a mineral reservoir which acts as a buffering system for such essential electrolytes as Na^+ , CO_3^- , and Mg^{++} as well as participation in homeostatic control of Ca^{++} , PO_4^- , and pH. Major shifts in electrolyte balance must be presumed to invoke regulatory mechanisms which are poorly understood. The secretions of the parathyroid glands and vitamin D can be considered to have important functions in these regulatory mechanisms and are considered in detail in the following chapter.

(Neuman and Neuman 1958, pp. 135-136)

The book goes on to consider calcification mechanisms vis-à-vis the role of phosphatase, ester phosphates, and of glycolysis, and, in the case of vitamin D, a role of a renal-induced phosphaturia. There was much that was speculative in this presentation. Much has been subjected to further experimental work by these and other authors. Further details would carry us too far beyond the central theme of this chapter, viz., ways in which the research described in this book involved investigations of mechanisms. Suffice it to say that the work still goes on, much of it in laboratories that were involved with the original MED research operations. The work with radium uncovered quite early the nonuniformity of distribution of isotopes in bone on both a macro- and a microscale and stimulated attempts to uncover mechanisms (chapter 1). In the post-World-War-II years, particularly with needs to understand the story with the isotopes from fallout, such as those of strontium, real advances were made in working out the mechanisms of mineral metabolism in bone. An early example is seen in work at Berkeley (chapters 6 and 8), for example; Jones and Copp (1948).

The Argonne National Laboratory (ANL) group was especially active with studies of bone, in addition to those at Rochester and Berkeley. The Argonne semi-annual reports carried a continuing series of papers on the subject during the middle to late 1950s. Their authorship is given below, and the subjects are given in the reference section (Marshall, Rowland, and Jowsey 1956; Marshall, White, and Cohen 1957; Rowland and Marshall 1958; Marshall and Rowland 1958; Marshall and Finkel 1959; Marshall 1960a,b; Marshall and Finkel 1960; Rowland 1960, 1961; Marshall 1968; Marshall 1970). Published versions can be found in Marshall (1962), and the often-quoted ICRP Publication 20 (see below). Another early example comes from Rochester (Boyd, Neuman, and Hodge 1958). There

are many others laced through this and other chapters. There can be no doubt that all of this pertains as much to the mechanisms involved as to its original objective, bone dosimetry.

The obvious differences in gross and microscopic localization in bone of plutonium and the actinides compared to radium and calcium led to much mechanistic work. Major interest centered for many years on just how the surface-seeking actinides like plutonium attached to bone. The MED work described in chapter 8 established clearly that plutonium deposited on bone surfaces. It was assumed at first to be combining with the organic material of the matrix. There were inconsistencies, however, that led to doubts about this. In the late 1950s, the researchers at Utah attacked the problem with a relatively new technique that permitted the preparation of good autoradiograms of *undecalcified* bone. In rachitic rats, Jee and Arnold (1962) proved that plutonium IV citrate readily passed through the uncalcified osteoid and deposited on the underlying calcified bone surfaces. This accounted for the major portion of the plutonium deposited. A small portion did become bound to the organic matrix. Other work showed that this phenomenon was not limited to rachitic animals and that the early idea that plutonium deposited exclusively on bone surfaces, because it combined with the organic matrix, is wrong.

An excellent summary of the behavior of plutonium in bone at the microscopic level is contained in the comprehensive chapter by Dame Janet Vaughan and her colleagues (1973), especially the section on the pattern of ^{239}Pu distribution in the skeleton (pp. 397-421), the theory and technique of alpha dosimetry with particular reference to the skeleton, and radiation dose measurements from deposition of ^{239}Pu in the skeleton written by Betty Bleaney (pp. 424-451). There are others, but this will suffice.

Relatively recent work on the microdistribution of plutonium is seen in work by Schlenker and Oltman (1981). This was presented at the Snowbird (Utah) Actinide Workshop. Also of interest is earlier work presented at one of the University of Utah symposia (Schlenker, Oltman, and Cummins 1976). These experiments applied autoradiography and alpha-particle spectrometry to samples of bone from three of the plutonium injection cases described in chapter 7. Distinct patterns of distribution could be identified on the basis of fission tracks in the autoradiograms. The kinds of deposits identified were:

- (1) Buried surface deposits—These are associated with bone surfaces that were exposed to plutonium and subsequently covered by the formation of new bone. They often appear as intense bands of fission tracks that are covered by bone layers several tens of microns thick.
- (2) Labeled bone volume deposits (LV)—These are associated with bone volume formed while plutonium was present in the blood. The labeled volume produces a relatively high density of fission tracks compared with the unlabeled bone volume (UV). Tracks produced by the latter are due only to natural ^{235}U . Labeled and unlabeled volumes are always separated by buried surfaces.
- (3) Bone surface deposits (S)—In this category, we include only the deposits on the bone surfaces now in existence; deposits on buried surfaces are specifically excluded. Two subcategories are also important:
 - (a) Deposits on the surfaces of labeled volumes (S(LV))—These begin to accumulate after bone formation stops and are easy to recognize in the autoradiographs because the adjacent bone volumes show relatively high densities of fission tracks.

(b) Deposits on the surface of unlabeled volumes (S(UV))—These accumulate on bone that was formed before injection. The adjacent bone volumes show relatively low densities of fission tracks in the autoradiographs. (Schlenker and Oltman 1981, p. 200)

The conclusions from this work give a glimpse of the complexity of behavior of the actinides in bone, the importance of time, and the gross oversimplification of designating bone-seeking radionuclides as either a "surface seeker" or a "volume seeker," as is done for purposes of standard-setting. The conclusions as given by Schlenker and Oltman are as follows:

- (1) In the absence of bone remodeling, concentrations are not greatly different on endosteal, Haversian canal, and periosteal surfaces of long-bone midshafts, 17 months after injection.
- (2) Endosteal surfaces in the axial skeleton show higher concentrations than do the surfaces in the appendicular skeleton at 15 and 17 months post injection.
- (3) The thickness of volume deposits formed by appositional growth exceeds the α -particle range. Thus, the deposits are "infinitely thick" for dosimetric purposes, and existing surface cells are shielded from intense buried surface deposits.
- (4) Surface deposits are so thin that, for purposes of dose calculation, they can be considered to have zero thickness.
- (5) The secondary surface deposits are of considerable dosimetric significance, even when the plutonium is primarily deposited in the volume of bone. (Schlenker and Oltman 1981, p. 206)

A further analysis pertaining as much to macroscopic as to microscopic distribution, but based upon events at the micro level, was given by Larsen, Oldham, and Toohey (1981) at the same actinide workshop. They are typical of a host of investigations bearing on differences among bones from different parts of the body and within a given bone. A portion of the abstract from their presentation is given below:

The concentrations in most axial bones were factors of 2 to 4 higher than the average in the entire skeleton; the concentrations in the skull bones were about the same as the average, and the concentrations in the appendicular bones were a factor of 2.5 to 8 lower than the average.

Within any particular bone, the concentration in the trabecular portion was always higher than that in the cortical portion; amongst whole bones, plutonium concentration was not correlated with degree of trabecularity. The bone that could be readily taken at autopsy and whose plutonium concentration closely approximates the skeletal average is the clavicle.

(Larsen, Oldham, and Toohey 1981, p. 191)

Again it must be noted that such differences point out that the setting of standards for bone, as if it were a monolithic entity, can be subject to considerable error.

Microanalytical studies of distribution of both ^{226}Ra and ^{239}Pu have become exhaustive. A good recent example is a report by Bruenger et al. given at the International Conference on the Radiobiology of Radium and the Actinides in Man held at Lake Geneva, Wisconsin (Bruenger et al. 1983). The age at exposure has a significant effect on distribution and retention of both elements. The role of processes at the cellular level in these is analyzed.

Much detailed autoradiographic evidence for mechanisms of the changes in bone came from earlier work of the Utah group. Examples are Arnold and Jee (1957) on bone growth and osteoclastic activity as indicated by the distribution

of plutonium, and Jee and Arnold (1961) on the relationship between plutonium distribution and the sequence of histopathologic changes in bone.

The program with miniature swine at Hanford contributed also to the interpretation of mechanisms, as did the later inhalation work with beagles. An important feature described by Clarke (1962) is the role of circulatory changes. He was comparing ^{239}Pu , ^{226}Ra , and ^{90}Sr and found many qualitative differences in their action at the cell level. He noted considerable necrosis of the Haversian system with plutonium and linked it to blood vessel fibrosis. Thus, loss of osteon circulation caused by fibrosis of the medullary vasculature provided an indirect mechanism for the Haversian system necrosis. There are many other examples (see, for instance, the genesis of a polonium-induced lesion in kidney described in chapter 4) where interference with circulation by radiation-induced necrosis from the passage of the radionuclide through vasculature seems to be responsible for fairly wide-ranging effects.

A general review of basic microscopic phenomena in bone and their influence on dosimetry is contained in the monograph by Spiers (1968).

2. Uptake, Retention, and Models for Bone

Evident throughout chapters 7 and 8 and in parts of chapter 1 was the fact that the retention of radionuclides in bone could frequently be described by a power function of time. Since the power function was thought to have no physiological meaning, whereas exponential functions could be associated with compartmental models, there were many attempts to analyze the kinetic data for bone into several compartments and to identify these compartments anatomically or functionally. This has not been notably successful, but much auxiliary information about bone was obtained. The power function kinetics led to development of the only coherent model for behavior of a group of radionuclides in bone—the model for the alkaline earths—usually attributed to Marshall (1963 and numerous references given in the previous section), although it appeared also as a committee report under ICRP auspices (ICRP 1972). Nuances of this and other models are described in Spiers's book, and the need for a comparable model for the actinides was discussed in chapter 16.

It has been proposed that the power function model (McLean and Budy 1964, p. 102) may be more than empirical. Marshall postulated that it can be viewed as a statistical representation of a complex system in a state of dynamic equilibrium and not necessarily a resultant of a set of simultaneous exponential functions of time.

Mineral metabolism, in general, has been markedly advanced by correlates from the researches on bone. Naturally, the homeostasis of calcium has been central to the mechanistic work since it is among the most precisely controlled elements in the body. However, the gathering of information has extended to all moieties involved in mineral balance, both endogenous and exogenous. Numerous examples have been presented throughout the pages of this book.

Plutonium deposition kinetics and their mechanisms have been a central theme. These were analyzed by Durbin, Horovitz, and Close (1972) for the 1971 Hanford symposium on biological implications of the transuranium elements. A digital computer program was utilized to describe the transport to bone and deposition of Pu(IV) citrate . This built upon biochemical research, some of it described elsewhere in this book, elucidating the fact that plutonium is carried in the blood in part in combination with an iron-containing protein, transferrin (Taylor 1973), some of it carried unbound, and that several compartments could

play a role. The abstract of the presentation by Durbin, Horovitz, and Close summarized the proposed mechanisms as follows:

A conventional kinetic model was constructed to describe the transport and deposition of intravenously injected Pu(IV) citrate in the rat. A digital computer program (MIMIC) was used to generate numerical solutions to the differential equations representing the compartment model. Tissue data and information on the rate of Pu-protein binding in plasma were drawn from published sources. The model consisted of two blood compartments, unbound Pu (Pu_f) and protein-bound Pu (Pu_b), assumed to be bound for the most part to the Fe-carrying protein, transferrin (TF); two extracellular fluid (ECF) compartments, Pu_f and Pu_b ; and four effectively non-returning sinks: liver, skeleton, soft tissues and excreta.

The implications of the solution of the model led to the following working hypotheses: (a) Pu_f reacts with protein, presumably TF, in ECF as well as in plasma. The Pu-TF complex is the most likely form in which diffusible Pu is mobilized from parenteral injection sites, and the most likely form in which orally administered Pu is carried once it reaches the plasma. (b) Little, if any, Pu_b is excreted or deposited in the liver. Formation of the Pu-TF complex is probably not a necessary preliminary to liver deposition of diffusible Pu. (c) Both Pu_f and Pu_b are sources of Pu deposited in bone. The surface of the reticulocyte (where Fe is released from the Fe-TF complex) is considered the most likely site of dissociation of the Pu-TF complex. Pu released at that site could either recombine with TF and recirculate as Pu-TF, effectively prolonging Pu circulation, or recirculate temporarily as Pu_f providing the necessary feedback of Pu_f , or diffuse to the most readily accessible bone surface. (Durbin, Horovitz, and Close 1972)

The rates of calcium accretion and loss in various bone diseases have been studied quite carefully and the findings applied to possible mechanisms. The rates vary from considerably above normal (Paget's disease, metastatic carcinoma, fracture, Cushing's disease, hyperthyroidism, and hyperparathyroidism) to considerably below normal (vitamin-D-deficient rickets, hypothyroidism, hypoparathyroidism). The detailed mechanics for these changes in calcium accretion are only partly worked out. Some of the original data can be seen in Bauer, Carlsson, and Lindquist (1961) and in Dymling (1962).

A useful review of the literature on bone during the "growing years" of our subject can be found in the annotated bibliography on strontium and calcium metabolism in humans and animals compiled by Wasserman and Comar (1961). The subject index from this volume, containing 1,161 references is reproduced as note 1 at the end of this chapter. If one considers that this is now over twenty years old, the volume and variety of studies on mineral metabolism accumulated even to that date can be gauged. Spin-offs to mechanisms are legion.

D. Whole-Body Counting

One of the least invasive techniques for measuring radioisotopes in the body is the so-called whole-body counter. It began around problems of bone seekers, with the methods developed for determining the radium burden of dial painters and patients (chapter 1). The methods of the 1930s were sensitive only to about 0.1 to 0.2 μg radium equivalent. The Los Alamos 4- π liquid scintillation counter was sensitive to about 0.0001 μg of radium equivalent or 1% of the total body ^{40}K . The sodium iodide crystal counter at ANL was sensitive to about 0.0003 μg radium equivalent. Naturally, such sensitivity led to many uses beyond determination of radium equivalents. Among these was a considerable amount of investigation into the metabolism of body potassium in adults and children, the

changes with age, determination of body muscle mass, etc., in health and disease. Nearly every whole-body counter, even though financed for practical jobs of determining body burdens of radium or the radionuclides in fallout, was useful for fundamental investigations of mineral metabolism.

A relatively early compendium on whole-body counting was the result of a symposium, *Radioactivity in Man*, held at Vanderbilt University and published in 1961 (Meneely 1961). In addition to reviews of the methodology and its pitfalls, some of the applications to basic biology and clinical medicine are given, along with the practical applications discussed in earlier chapters. The kinetics of retention of, for example, ^{60}Co -labeled vitamin B_{12} were found to be quite different in chronic myelogenous leukemia compared to normal; the retention of ^{85}Sr was quite different in osteomalacia, osteoporosis, and hyperparathyroidism; the absorption of iron from the intestine was quite different in iron-deficient from normal individuals.

A center for applications of the whole-body counting technique to various mechanistic problems has resided over many years in the Medical Division of Brookhaven National Laboratory (BNL) under the direction of Stanton H. Cohn. It began with collaborative work on man with Herta Spencer (see earlier chapters) for investigations into the turnover of ^{85}Sr , influence of dietary stable strontium and calcium on the turnover of bone-fixed ^{85}Sr , and the like. Soon Cohn's studies extended to the turnover of other fallout radionuclides; to studies of iron and vitamin B_{12} turnover; movement of iodine in pregnant and non-pregnant women; composition of various types of bone and the events relevant to mineral metabolism in osteoporosis, thalassemia, Cushing's disease, chronic renal failure, aging, even some forms of cancer. With the decrease in interest in body burdens of fallout radionuclides in the population, the country's whole-body counters have supplied mechanistic bases for a host of biochemical and physiological investigations.

E. Carcinogenesis

It has been said that ionizing radiation is truly a universal carcinogen because in all forms and under a large variety of circumstances one of its long-term sequelae is cancer. A large effort has gone into research on the mechanisms of radiation carcinogenesis. Much of it has employed external radiation sources, since they are easier to handle than deposited radionuclides. Yet, the almost ubiquitous occurrence of cancer of both bone and soft tissue from deposited radionuclides in sufficient quantity for sufficient time has led to many mechanistic investigations with them. We will review some samples in this section that can be considered closely related to the theme of this book. A recent overview compiled by the U.S. Department of Health and Human Services (DHHS 1984) using abstracts is about equally divided between external radiation sources and internal emitters.

General mechanisms of radiation carcinogenesis can be divided into at least four overlapping classes: (1) those involving local origin of the initiating events and the promotional events; (2) indirect changes through regions remote from the site of irradiation (part of the set of phenomena designated as "abscopal"); (3) cases in which the initiating events are induced by radiation, but the promotional events occur largely by other means; and (4) those in which the initiating cellular events are not caused by radiation, but radiation induces the promotional events. While much of the evidence comes from studies using external

radiation sources, there have been important contributions from research with deposited radionuclides. Nearly all of them bear on the role of promotional events, for it seems clear that a single hit from almost any ionizing radiation source may, under the proper circumstances, produce a somatic mutation that could initiate the carcinogenic process.

The accumulated evidence indicates that some radioisotopes that have rather general distribution in the body (e.g., tritium, radiosodium) produce a wide variety of tumors in different tissues. Others (e.g., polonium and thorium) which produce copious amounts of radiocolloids and thus settle in elements of the RES, result in a variety of cancers attributable to the RES. Others that localize in bone or lung or thyroid produce almost entirely tumors or cancers of those organs, except, for instance, where the deposited radioactivity also irradiates surrounding structures. This holds even though the radionuclides in their early stages of distribution may have passed through many other tissues. Thus, the effects seem to be confined largely to the tissues of longer-term retention. The presence of an abscopal effect seems minimal or absent with the highly or moderately localized radionuclides, in contrast to the situation with whole-body radiation or widely dispersed radionuclides. An exception is those situations where endocrine glands are involved, either primarily or secondarily.

A more detailed statement of possible mechanisms for carcinogenesis from radionuclides is contained in a review of the pathogenesis of radionuclide-induced tumors by Casarett (1973) given as part of a Hanford symposium on radionuclide carcinogenesis (chapter 8). In summary, they can be set down in the author's words:

Carcinogenic mechanisms may include events occurring at any time from the prezygotic stage to the time of the beginning of malignant neoplastic proliferation.

The cellular initiating events are thought to be mutations or chromosomal aberrations caused by physical, chemical, or biological (e.g. viral) agents. They involve:

1. Prezygotic (inherited) germinal-cell mutations or chromosomal aberrations persisting in the formation of the zygote and transmitted to many daughter cells of many kinds through the cell proliferation in subsequent development of the organism.

2. Postzygotic somatic-cell mutations or chromosomal aberrations acquired throughout life, with variable degrees of transmission to daughter cells, depending upon the cells acquiring the aberrations and the time of this acquisition with respect to the development of the tissues and organs of which they are parts.

The promoting events are variable for cancers of different tissues or organs. They may be caused by physical, chemical, or biological agents or by pathologic or basic aging processes and may include:

1. Local tissue damage and disorganization, i.e., so-called "precancerous lesion" or "chronic inflammation" in sites of origin of tumors, consisting of parenchymal degeneration and hypoplasia, vascular and interstitial fibrosis, and continued abortive or disorganized attempts at regeneration by remaining parenchymal cells.

2. Normal or enhanced hormonal proliferative stimulation of neoplastically potentiated cells in tissues under special hormonal control, especially in endocrine glands and gonads.

3. Depressed immune competence, which may be especially important in viral carcinogenesis and possibly in carcinogenesis in general.

It is apparent that there are two general classes of mechanisms of carcinogenesis, depending upon whether or not the required promotional tissue changes are located largely in the same locale as the potentiated cells that will originate the cancer.

(Casarett 1973, pp. 1-2)

The fact that we cannot yet separate specifically the two major categories given above bespeaks the complexity of the problem. Nevertheless, some starts have been made, as we will see presently.

The progress of histological changes in both humans and animals has been worked out in detail. Addressing the changes seen in humans with radium, mesothorium, and radiothorium, Casarett (1973) describes them as follows:

The prominent histopathologic changes preceding the appearance of the osteosarcomas consist in the formation of atypical osseous tissue around trabeculae of cancellous bone, the formation of an acellular fibrous tissue in the intertrabecular spaces, and the development of areas of destruction of compact bone with replacement of bone by fibrous tissue. Neoplasms develop in or near areas of proliferating fibrous tissue and atypical osseous tissue. These regions are found especially at the ends of the bones, where atypical bone tissue is most likely to form.

Concerning the changes noted in the large animal experiments, Casarett says the following:

Studies of the bone of dogs receiving single intravenous injections of ^{239}Pu , ^{226}Ra , ^{228}Ra , or ^{228}Th have shown that the histopathologic changes preceding the development of osteosarcomas were similar to those in the radium-bearing human beings. High radiation doses altered the vasculature and circulation, caused bone necrosis and bizarre osteones, bone resorption, reduced bone formation, and marrow fibrosis.

The histopathologic changes preceding the development of osteosarcomas following internal administration of radiostrontium tend to be more advanced in the ends of bones, near regions of endochondral bone formation, and include in their sequence damage and hypoplasia of bone marrow; damage of growing cartilage in regions of endochondral bone growth; development of endosteal tissue hyperplasia and intensified remodeling of bone; development of fibrous hypovascular marrow containing scattered atypical connective tissue and osteogenic cells; subsequent retardation of osteogenesis and bone modeling; dystrophic changes in the osteogenic tissue; the appearance of amorphous and coarse-fibered calcified material in the marrow spaces; production of coarse and atypical immature osteoid or osseous structures in the marrow space; the appearance of atypical, free osteogenic cells with pleomorphic or anaplastic characteristics in the acellular, hypovascular marrow near the abnormal bone or osteoid formations; neovascularization of this tissue; and finally, proliferation of this osteogenic tissue in cancerous fashion, with invasion of nearby structures and metastasis.

(Casarett 1973, p. 12)

Many studies have looked for additive or synergistic effects of radiation and chemical carcinogens and have found both. In some instances, the mechanism of action of the two carcinogens seems to be different. In other instances, there are not obvious differences. Both agents seem to be mutagenic, and this has supported theories of carcinogenesis based on somatic mutations.

Much of the early mechanistic work with radionuclide carcinogenesis concentrated on the influence of the physical and chemical form of the radionuclide, the physical and biological half-lives, the type of radiation (i.e., LET), age, physiologic state, and the like. Except for work pertaining to the uranium miners, formal searches for adjunctive agents were not numerous. It appears that Miriam Finkel and her colleagues conducted some of the earliest experiments (begun in 1961) to search for a possible viral component in tumors induced by radionuclides (see, for example, Finkel, Biskis, and Jinkins 1966; Finkel and Biskis 1969; Reilly and Finkel 1971; Finkel and Reilly 1973). They identified virus-type particles in electron micrographs of spontaneous tumors in mice, injected

the particles into newborn mice, and sarcomas were induced. They called the virus "FBJ" virus (for Finkel-Biskis-Jinkins). They then began a series of experiments in which FBJ virus was injected into newborn mice, and ^{90}Sr was injected later into some mice at different ages. They could distinguish between ^{90}Sr and FBJ tumors by their site of origin, endosteal surfaces for ^{90}Sr , periosteal or parosteal for the viral tumors. Strontium-90 had little effect on FBJ tumors, but the pattern of ^{90}Sr tumors was markedly affected by the virus. Furthermore, the ^{90}Sr -induced tumors were found to contain particles of the virus.

Naturally, association does not prove causation. That has yet to come. Also, there were complications. The tumors induced by extracts from ^{90}Sr -induced osteosarcomas were frequently benign (osteomas) rather than malignant (osteosarcomas), and frequently the extracts were inactive. Also, there were different and larger particles present in some instances, called "RFB-osteoma virus" (for Reilly-Finkel-Biskis), the time of onset of the tumors was different, etc. Yet, on balance, the finding of virus-like particles in every ^{90}Sr -induced osteogenic sarcoma led the authors to conclude there was some meaning in the association.

Some work from Hanford with miniature swine pointed to an association between a virus and ^{90}Sr -induced leukemias. In the swine, there were many more leukemias associated with the daily ingestion of ^{90}Sr than in many of the intravenous injection experiments with bone-seekers such as radium and plutonium. Frazier, Ushijima, and Howard (1970) found virus-like particles in lymph node, spleen, kidney, liver, and blood plasma in the swine bearing leukemia. None were seen in control animals.

Suppression of immune responses in chronic ^{90}Sr administration has also been demonstrated in miniature swine. Such suppression has frequently been implicated as one step in carcinogenesis and is not unusual after radionuclide administration.

Naturally, as alluded to earlier, radionuclides that deposit close to or in endocrine organs may induce cancer partly by upsetting the endocrine balance of the body. This has been particularly noted for iodine deposition in the thyroid. It can bring about not only the changes referable to thyroid function, but effects on pituitary function as both a normal reaction of the pituitary gland to the stimulation caused by the loss of thyroid hormone and direct radiation from the thyroid gland. Thus, tumors may be induced indirectly by the attempts of an endocrine gland to correct for deficiencies in function of a gland it normally controls. These may, in turn, cause more widespread endocrine disturbances at still other sites, e.g., parathyroid, adrenal cortex, ovary, uterus, mammary gland.

Another phenomenon with mechanistic overtones concerns the still-puzzling apparent differences between a radiation dose delivered by a deposited radionuclide and the same calculated radiation dose delivered from an external source. For example, in the case of the longer-lived isotopes of iodine that are less effective than external radiation, it is speculated that their low energy and nonuniform distribution leave significant areas of follicular colloid undamaged. This might account for the lesser effect of these iodines compared to a comparable dose from an external source. Let us not forget, however, that absorbed doses in each case are calculations and not actual measurements at the target cell. Thus, the difference must be viewed as likely but subject to more sophisticated dosimetry.

Much more could be cited to illustrate the contributions of research with radionuclides to the understanding of mechanisms of carcinogenesis, but it would not introduce anything qualitatively new. On balance, it must be said

that much of the work raises as many questions as it settles. The inherent complexity of the genesis of cancer is not made simpler by introducing the complexities of dosimetry, microdistributions, and kinetic behavior of deposited radionuclides at both the cellular and tissue levels.

F. Respiratory System

1. Generalities

It must already be abundantly clear from chapters 9 and 10 and section I of this chapter that the efforts of the internal emitter establishment in the inhalation field were enormous. It is also clear that they led the way for inhalation toxicology in general. Correlates to mechanisms in the respiratory tract have been significant and very broad. They range from situations where the radioactive material served primarily as a tracer for the description of kinetics, particularly of clearance from the lung, to intimate cellular mechanisms. We will cite only a few examples here since much was presented in the inhalation chapters.

General contributions to mechanisms in the respiratory tract developed from the fact that much of the inhalation work was concentrated in centers (chapter 9). The individuals gathered in these centers had roots in respiratory physiology, pharmacology, and pathology, or industrial hygiene and aerosol physics. They were keenly aware of the problems of chemical toxicology as well as of radioisotope toxicology. Thus, the groups at Rochester (the earliest), Hanford, New York University, and Lovelace Inhalation Toxicology Research Institute produced much information bearing on the basic mechanisms in the respiratory system, some of it without even mention of radionuclides.

From the Rochester center, there came the first quantitative appreciation of the role of particle size. Later there was development of general portrayals of the mechanisms of deposition and clearance in twin reviews by Morrow (1960) on deposition and by L. J. Casarett (1960) on clearance, evaluation of the basis of the respirable dust concept (Morrow 1964), and much general aerosol physics and technology (Mercer 1973). On an even broader plane, Morrow chaired and Mercer was a key member of the task group of the ICRP that worked out the extensive and complex lung model now in general use (TGLM 1966; also ICRP 1979). In order to prepare the tables and graphs for this document, it was necessary to select figures for the clearance rates, make various computations from experiments for a large variety of elements in different chemical forms, and to depict deposition in different parts of the respiratory tract. This model, while titled "for internal dosimetry" and thus implying radionuclides, can be applied equally well to nonradioactive dusts and should be. As still another example, we might mention that J. K. Scott and J. N. Stannard, from Rochester, took part in preparation of the National Academy of Sciences (BEAR) report on effects of inhaled radioactive particles (NAS 1961), a report that focused considerably on mechanisms.

From Pacific Northwest Laboratory (Hanford) came careful analyses of the histopathology of areas of the respiratory tract subjected to inhaled radionuclides, including mechanisms of carcinogenesis; much interest in the role of pulmonary phagocytic processes; the effects of adjuvants such as ore dust and cigarette smoke; and, in recent years, extensive studies involving other types of energy generation. The Battelle group at Hanford produced several definitive

reviews that included discussion of mechanisms.^(a) The Hanford symposium on inhaled radioactive particles and gases, chaired and edited by W. J. Bair (1964), devoted a special session to review of the biology of the respiratory tract with papers from several laboratories. Several reviews on plutonium, e.g., Bair et al. (1973); Bair, Richmond, and Wachholz (1974); Bair (1974); Bair (1977); Park, Bair, and Busch (1972); Sanders (1969, 1970, 1972); Sanders and Adey (1970); Sanders and Park (1971); Thompson (1967); and many others that were directed primarily at behavior of inhaled materials included correlates to mechanisms. More recent mechanistic discussions sponsored by the Battelle group include *Radiation and the Lymphatic System* (Ballou 1976), *Pulmonary Macrophage and Epithelial Cells* (Sanders et al. 1977), and *Pulmonary Toxicology of Respirable Particles* (Sanders et al. 1980). Furthermore, W. J. Bair was a member of the relevant BEAR committee and chaired the ICRP task group that produced Publication 31, *Biological Effects of Inhaled Radionuclides* (ICRP 1980). An entire section of this report is devoted to "Tissues at Risk," but generalizations are not yet possible. This is not surprising when one considers that there are more than forty cell types recognized in the lungs and accessory respiratory structures, unevenly distributed, and not isolateable for a cause-effect examination by current methods.

The Lovelace center contributed to mechanisms especially in aerosol physics by the development of monodisperse aerosols that could be used routinely; by studying the influence of physical and chemical state and also of dosage regimen on behavior and ultimate effects of a variety of radionuclides; and, more recently, by extensions to chemical toxicology. They also went deeply into modeling using both computer-generated models and plastic casts of animal lungs. The latter were developed in such exquisite detail that many of the anatomical approximations made from autopsy material could be checked and modified. During his tenure at Lovelace, R. G. Thomas prepared a comprehensive review of the influence of aerosol properties on gross distribution and excretion of radionuclides (Thomas 1964). Among other correlations he made was a log-log (i.e., power function) plot of the time since exposure and the ratio of concentration in lymph nodes to that in lung. The ratio varied from 0.01 to nearly 100, increasing with time. This was a composite plot using four different radionuclides, different forms, and different species. He also reviewed the important role of carrier in retention, a subject much investigated at Lovelace, as well as Hanford. Some drastic effects of carrier could be demonstrated, particularly in experiments where the carrier was the stable form of the radioelement. Since the effect was to reduce retention of the radionuclide at high concentrations of carrier, it was speculated as being due to mass law effects. Also discussed was the frequent finding that even quite insoluble aerosols seem to contain a small but definite absorbable fraction. This led to speculation that there was a mechanism of uptake into the respiratory tract different from those normally involved. Alternatively, there could be a small absorbable fraction normally present that soon became fixed in lung tissue. Other features of the Lovelace contributions to mechanisms are evident in chapter 9 and in subsequent parts of this chapter.

The New York University (NYU) center was deeply involved in the mechanisms of behavior and transfer of fallout radionuclides, as we saw in the

(a) Many of these involved work from several laboratories, but are mentioned here since Battelle was the focal point.

chapters on the environment (especially Eisenbud et al.). Altshuler and Laskin were especially involved with mechanistic aspects of aerosol generation and behavior and with lung modeling. Along with others, they studied the reaction of lung to implanted sources. N. Harley was much involved with possible mechanisms of action of radon and daughters in the respiratory tract. The laboratory director, N. Nelson, was at the forefront of ideas about pulmonary carcinogenesis, as was R. Albert. Best sources of literature are the NYU annual reports cited in earlier chapters.

Occasionally, representatives from the industrial hygiene centers took part in discussions of respiratory mechanisms among the radionuclide people. A good example is the review by Paul Gross (1964) from the Industrial Hygiene Foundation in Pittsburgh on pulmonary deposition, clearance, and retention. Also involved were investigators from the United Kingdom with principal orientation toward nonradioactive aerosols (e.g., C. N. Davies—coal dust). L. Dautrebande from Belgium, father of the medical aerosol, who spent several summers working with the Rochester group, also shared experiences with the internal emitter toxicology people and wrote a comprehensive review on aerosols (chapter 9).

2. Some Details Regarding Pulmonary Radiotoxicology

Chapters 9 and 10 include so many specifics from the inhalation work that bear on mechanisms that little more needs to be said. For the purpose at hand, a few salient points will be reiterated:

a. The role of particle size was of both immediate, practical, and mechanistic import. The effects of particle size on deposition have now become firmly established. Effects on clearance and on toxicity are still found to be somewhat variable, with almost opposite effects seen depending on circumstances (Thomas 1964, and work cited therein and continuing work since). In general, the clearance rate for smaller particles was found to be faster than for large particles, except for material entrapped in upper respiratory passages or pulmonary lymph nodes.^(a) As a result, the translocation from lung to other tissues can be a function of particle size, and, sometimes, with very small particles, tissues other than lung contain the highest concentration even of highly insoluble materials. Toxicity is, in general, greater for smaller particle-size ranges, as described in chapter 9, but this is not universally true. This seems logical where toxic effects (or binding phenomena) are related to surface area, but other explanations must be involved for some situations.

A very common statement among those measuring air concentrations is, "The particle size is . . ." or they ask the question, "What is the particle size?" These are shorthand expressions. Except for the special circumstance of monodisperse aerosols, never encountered in nature or in the industrial environment, the aerosols have a range of particle sizes. The figure given is usually a median and must be accompanied by a statement of the standard deviation. Aerosols with identical median diameters, but quite different standard deviations, will behave differently in the respiratory tract, and many even exhibit different toxicities. The proper question is, "What is the particle size distribution?" However, habits are now ingrained, and all that can be asked is that anyone concerned with pulmonary radiotoxicology never forget that there is essentially no such thing as "a" particle size for practical or mechanistic purposes.

(a) Ciliary transport rate does not seem to be clearly related to particle size.

As described in chapter 9 and presented early by Stannard (1959), the greater toxicity of smaller particle sizes may have a unique explanation in the case of aerosols of radioactive materials. In chemical toxicology, the effects are likely to be proportional to the mass of the material deposited. Carriers (or vector aerosols) are not of great importance except for highly toxic elements. With all but very-low-specific-activity radionuclides, the mass present is usually very low. The activity is carried largely on nonradioactive particles that act as carriers or vectors. There appears to be a tendency for radioactive materials to attach somewhat preferentially to the smaller particles. Also, there are many more smaller particles in an aerosol of a given mass median diameter. As a result, distribution of mass of the vector aerosol may bear little relation to the distribution of activity and thus to the distribution of effects. To compensate for this, radioactive aerosols are commonly characterized in terms of activity median aerodynamic^(a) diameter (AMAD). While regularly appreciated by those with considerable experience, the importance of measuring and expressing the characteristics of radioactive aerosols in terms of activity should be remembered by all, even in routine applications.

The amount of research in aerosol physics behind these and other specific phenomena of basic importance is large, as reviewed in earlier chapters.

b. Before we get too carried away with the importance of particle size, we must recall that changes in physiological parameters, such as tidal volume, respiratory rate, ventilation rate, and the like can have as much influence on deposition as the particle size distribution. This is discussed in chapter 9 and in the ICRP lung model description (ICRP 1979).

c. Another fundamental point derived from the work in pulmonary radiotoxicology concerns solubility. As the work unfolded (chapter 9), it became abundantly clear that behavior in the respiratory tract bore little relation to solubility of a given compound in water. Substances that were hardly soluble at all in water were sometimes found to be cleared rapidly from the respiratory tract. Conversely, some fairly soluble substances were found to be rapidly bound or fixed. Much basic research was done to determine the differences between body fluids and inorganic media in determining the solubility of inhaled materials. Simulants for lung fluids have been developed and used, particularly by Raabe in his days at Lovelace (chapter 9). Nevertheless, no perfect simulant has yet been developed. Fundamental mechanisms of "solubility" in the respiratory tract need further attention.

d. Much work has been done on the biochemistry of the lung. Some of it came from representatives of the efforts in pulmonary radiotoxicology. It is purposely neglected in chapters 9 and 10 because there seems to be little obvious correlation to the behavior of radionuclides or their effects. However, the ultimate effects may rest heavily on some of the nuances of this complex lung biochemistry.

e. The generation of a sophisticated lung model for the behavior of inhaled aerosols was the result of many years of constant attention to pulmonary mechanisms. Even during the MED days, one objective of the work was said to be the development of lung models. The current ICRP model represents a culmination of such work, but it does not stand alone. Alternative models have been suggested and can be used for specific situations. Some of these involve differences

(a) "Aerodynamic" to indicate that the particle behaves aerodynamically like a spherical particle of that diameter.

in detail. Others address the need for application to broader segments of the population and, thus, tap into the reservoir of physiological and pathological information concerning the very young, the elderly, the bearer of a pulmonary disease process, etc. Thomas (1984) is developing a lung model for children of all ages that can accommodate any particle diameter or density, physiological variables, and the like.

f. The pulmonary lymph nodes continue to pose a dilemma. They frequently accumulate by far the highest concentrations of radionuclide in the entire body. Yet, they seem to be far less prone to the development of cancer than many other structures. Only relatively recently have any cancers originating in pulmonary lymph nodes been described, and these are not frequent enough to negate the generalization regarding their apparent radioresistance in terms of carcinogenesis. However, lack of cancer production should not be equated to lack of effect. Profound necrosis of the pulmonary lymph nodes is common. What effect this has on the functions of the lymphatic system generally, and on the cells that happen to pass through, is not clear. As we saw earlier, a lymphocyte reflects where it has been.

G. Radiocolloids and Complexing

Throughout the attempts to understand the behavior of radionuclides in biological systems, there have been persistent indications that the materials were not always traveling as simple ions in solution. It began with consideration of aqueous solutions. The history was described by Schubert (1948). Two aspects were found to be of importance: the formation of complexes (see chapter 2) and of radiocolloids (see chapter 4).

In 1928, Paneth dialyzed water solutions of naturally occurring radionuclides against running water. He found that some passed through the membrane while others did not. He attributed the phenomenon to the formation of colloidal-sized aggregates in the solution. Others, including the influential Otto Hahn (1936), attributed the phenomenon to adsorption of the radioelements on solid impurities accidentally present in the solutions. In either case, a dilemma was posed since both the radioisotope and the "impurity" were in such low concentration that their solubility product should not have been exceeded. But Haissinsky (1934) had already stated, "one cannot apply to these compounds the usual conception of solubility and solubility products."

Appreciation of the importance of radiocolloids developed during World War II at both the Metallurgical Laboratory in Chicago and in Berkeley. As a result of the Chicago work, Schubert (1948) published experimental results along with the historical summary already cited. He described the radiocolloidal properties of some of the fission products using dialysis, ultrafiltration, ion-exchange adsorption, etc. He concluded that whether or not the aggregates were truly colloidal in nature, they behaved like colloids and were about 10^{-6} cm in diameter. Special cautions were issued not to let these phenomena complicate the reproducibility and interpretation of any results obtained using buffered injection solutions (the colloids are less "soluble" near neutral pH) and in interpreting *in vivo* phenomena.

Reports from Berkeley focused on the effects of these radiocolloidal phenomena on behavior of radionuclides *in vivo*. It seems to have started with observations that colloidal calcium phosphate (Jones, Wrobel, and Lyons 1944) was taken up by liver and spleen and was followed by work with some of the

rare-earth-type elements. Dobson et al. (1948) described the differential behavior of colloids of different sizes in mice, rats, and rabbits of elements such as yttrium, zirconium, lanthanum, and columbium. The effort was sufficient to lead to more than academic interest. It was considered possible to selectively irradiate different organs or tissues by manipulation of colloid particle size. Gofman (1949) gave details of the chemical principles and methods for preparation of the pertinent colloids and how they might be of clinical use. Incidentally, it became clear that the colloids once deposited tended to remain in situ for fairly extended periods.^(a)

Schweitzer and colleagues at the University of Tennessee (1952, 1953) called further attention to the importance of radiocolloids in solution and in vivo. There was much interest, generally, in the aggregates seen in lung and bone by autoradiography, whether or not these represented colloidal phenomena *per se*.

The tendency to consider *both* the phenomena in the injection solution and in the organism after injection continued for many years. For example, the Rochester group looked in some depth at the properties exhibited by ^{210}Po , both in vitro and in vivo. This work was described, in part, in chapter 4. A summary by Stannard and Casarett (1964), taken from the concluding comments of the polonium monograph (see chapter 4), tells the story succinctly. It is reproduced, in part, below:

SOLUTION CHEMISTRY AND RADIOCOLLOIDS

The first five papers (6-10) address the behavior of polonium-210 in vitro or in vivo by techniques intended to characterize its behavior as a "radiocolloid" and its combination with biologically important molecules. Using microfilters, Morrow, et al. (6) present data from our early experiments on solutions of polonium. Despite the somewhat preliminary nature of the study, it shows clearly that at physiological pH the element is largely present in a nonfilterable form. By contrast, at acid pH the element is in a more readily filterable form and behaves less like a colloidal hydroxide.

Subsequent studies (centrifugability, settling, etc.) showed properties consistent with the broad definition of a colloid, although the low concentrations of polonium prohibit application of such objective criteria as light scattering. The size may range widely (8), and the behavior may be greatly modified by the presence of complexers as shown in the carefully controlled in vitro experiments of Feldman and Saunor (10). . . .

Of major importance is the possibility that oxolation, after ololation, produces polymers that are accessible only to strongly penetrating complexers after their formation. Thus, once formed, these polymers may persist as entities through many subsequent treatments of the solution and even though initial periods in vivo.

The presence of complexers considerably reduces the number of larger aggregates in solution, which suggests that similar changes occur in vivo, and that the large aggregates do not persist indefinitely. This is exactly what has been found in the autoradiographic studies, both those reported herein (11) and the earlier study of Gallimore, et al. (12). Independent evidence for changes in diffusability is found in the results of Hursh (13) who showed increased dialyzability of polonium combined with BAL (British Anti-Lewisite) and in the basic chemical studies at Mound Laboratory and elsewhere (14). In fact, Stannard and Haydon (15) showed that BAL increased the absorption of orally administered polonium from the gastrointestinal tract, presumably by formation of a more soluble complex in the gut wall.

(a) As we will see later, the aggregates do break up with time, in the case of some elements at least.

The disappearance of intravenously injected polonium from the blood and its appearance in elements of the reticuloendothelial system (7) are consistent with behavior of a material of colloidal dimensions. There can be little doubt that aggregates do exist in the blood after intravenous injection, and that these are removed by and deposited in the reticuloendothelial system. There is ample evidence from autoradiography for their presence (11,12) in blood and tissues after intravenous injection and for their disorganization and disintegration within a day or two after deposit.

An important contrast in physical state in vivo is seen by varying the route of entry. The larger aggregates characteristic of early times after intravenous administration do not appear in blood or tissues after oral administration. They are seen in the gut, however. Thus, the contribution of the large aggregates is entirely absent after oral administration except for the gut wall itself. After inhalation, aggregates can be found in lymph nodes, lung, upper respiratory tract, gut, or phagocytic cells, but almost never in other tissues. . . .

The apparent localization may contribute less to the total radiation dose than might be predicted from casual observation. L. J. Casarett (11) points out that the single atoms or small groups of atoms, ubiquitously present in the tissue sections studied, are much less dramatically emphasized in the autoradiogram than the large aggregate. Careful track counts indicated that less than 20% of the total activity appearing in the autoradiogram was contributed by polonium in the larger aggregates. This was in tissues of an animal receiving "neutralized" solution intravenously and hence having a maximum of larger aggregates. Since the aggregates are disorganized within a few days in vivo, we must conclude that the "hot spot" problem is probably not of large significance, nor is this aspect of the physico-chemical state of the entering solution the primary factor in determining dose distribution except during the initial hours after administration. . . . The fact that colloidal properties such as filterability, dialyzability, centrifugability, and in vivo behavior could vary markedly as a function of pH in a manner similar to that found in macroscopic hydrosols supports strongly the view that true radiocolloids are formed, not just pseudo-colloids due to adsorption on impurities. Yet our data on the addition of foreign particles are not conclusive in eliminating a role of this process also. Both processes may occur and contribute to the general phenomena. In fact, the question may be raised as to whether such phenomena exist quite generally in dilute solution and can be seen with solutions of radioactive materials only because of the unique techniques for measurement of very small quantities inherent in such work. Thus the term "radiocolloid" may have no real meaning except with reference to the methodology. The phenomena may be present in most very dilute solutions whether of radioactive or stable isotopes." (Stannard and Casarett 1964. All references except Nos. 13 and 15 are cited in chapter 4. References 13 and 15 are cited in chapter 19. Each is by author and date rather than by number.)

The pertinent authorship and cryptic references for these citations is given below:

- (6) Morrow, et al., *Radiat. Res. Suppl.* 6:1-15 (1964)
- (7) Thomas and Stannard, *Ibid.*, pp. 16-22
- (8) Thomas and Stannard, *Ibid.*, pp. 23-28
- (9) Thomas, *Ibid.*, pp. 29-39
- (10) Feldman and Saunor, *Ibid.*, pp. 40-48
- (11) L. J. Casarett, *Ibid.*, pp. 93-105
- (12) Gallimore, Boyd, Stannard, *Anat. Record* 118:253-74 (1954)
- (13) Hursh, *J. Pharmacol. Exp. Ther.* 103:450-59 (1951)
- (14) Spoerl and Anthony, AEC Rept. TID-5221, Chapter 5 (1956)

- (15) Stannard and Haydon, University of Rochester Atomic Energy Project Report, UR-429 (1956)

It is somewhat puzzling that the role of radiocolloids has seemed to receive much less attention in recent years. This may be partly because biochemical binding to various moieties became of more compelling interest. Nevertheless, the fact that these phenomena probably play a role in much of the solution chemistry and biological behavior of nonradioactive materials as well as radioactive materials should have stimulated more detailed research into mechanisms than has appeared in recent literature. It is a very relevant correlation of physical chemistry to biology with emphasis on low concentration chemistry.

We need add little more to the discussion of the role of complexing, binding to cell constituents and cell surfaces in the pharmacokinetics of radionuclides. Examples are evident throughout this book, including the bulk of the chapter on therapeutic removal of radionuclides (chapter 19). Many of the apparent inconsistencies in metabolic behavior and "biological variability" we have noted may rest, in part, on variation in some of the phenomena of complexing.

H. Comments on Section II

Each sophisticated reader of this book would probably select somewhat different correlates to make between the researches reported in the several chapters and the topics chosen for this short section on mechanisms. There are, indeed, correlates to mechanisms throughout, even in some of the most practically oriented areas. The bases for this author's selections were twofold: (1) points that had not been made in the earlier textual descriptions, and/or (2) points that required emphasis by discussion separate from the detailed presentation of experimental findings. The author hopes that the examples are sufficient to give a broad picture of the ways in which understanding of mechanisms has grown from the research, whether or not it was primarily aimed at their elucidation. It should be clear also that the unfolding of mechanisms contributed to and modified the progress of all of the research, no matter what its objectives. Clearly, physiology and histopathology have had to be slighted in this review, primarily because there is so much that it is difficult to say anything without reiterating whole sections of the text. Let us hope interested readers have the patience to ferret these out for themselves in the individual chapters.

III. Unfinished Business

Many occasions have been taken in the text to point out needs for additional work or items that could not be considered sufficiently, or even at all. This section is intended to set out the highlights of some of these, sometimes in a more general context than on the occasion of the original, sometimes in addition to the original. They are presented in three parts that concern, respectively, things that could not be covered, general areas requiring further work, and specifics organized chapter by chapter.

A. Omissions

It has been emphasized that our coverage was biased to work in the United States (see preface). Despite the considerable length of this book, much work

done in other countries has had to be either described very briefly or omitted altogether. General references that include such research make up in part for this deficiency. Some areas where the effort was to a considerable extent, even preponderantly, in non-U.S. laboratories do not suffer from these sins of omission, and the review is essentially global (e.g., chapter 19). In others, there was nothing to report from other countries because at the time the United States was the only country that had the pertinent radionuclides in its possession. Extensive research in the USSR has had to be referenced primarily by citing reviews. Perhaps a companion volume to the present one emphasizing these omitted and truncated areas would be a worthwhile project.

Detailed methodological aspects of much of the research have had to be omitted or given very briefly. The two chapters on instrumentation are, perforce, quite general. There is no doubt that advances in instrumentation and methodology were key factors in the progression of the research, as can be appreciated from chapters 17 and 18. Unfortunately, there have been many occasions when important specifics for a given experiment have had to be omitted to save space. However, it may well be that even condensed descriptions of techniques, such as might have been possible in these cases, would present such a poor substitute for reading the original papers that the best service we can perform is to get the reader into the literature.

It must be emphasized again, as it was in the preface, that this book is a history, not a critical review. Except where rather gross errors or obvious misconceptions may have led to quite erroneous data or conclusions, the work has been described without attempts to extrapolate to what the results might have been if the work were to be done today. No doubt the range of experimental error might be less, the sensitivity of the determinations greater, and the reliability of the figures thus enhanced. This may be particularly true in the area of environmental measurements. Also, interpretations might be different in the light of present knowledge. Nevertheless, the primary thrust of much of what is reported in this book is not unduly dependent on precision of measurement. Some apparent dilemmas might be easier to resolve if the experiments had used today's methods and today's concepts, but we would not be reporting history if that were the case. Thus, the results have been presented in terms of what the authors and laboratories did, what their measurements showed in terms of the methodology used, and the conclusions drawn by those who did the work or reported it. On the whole, we must be impressed by what was done, sometimes under incredible pressure, frequently under the yoke of secrecy, and with evolving methodologies. Undoubtedly, there were cases where even the then-available methodology was not used as well as it might have been. Perhaps some future historian would like to pinpoint these for posterity. On balance, we must be impressed with the relative solidity of the major conclusions of these decades of work.

B. Needed Additional Work

1. General

Before we proceed, a general comment is needed. If one word could be used to epitomize the needs of the future in this field, it would be mechanisms, *mechanisms*, **mechanisms**. The preceding section gave glimpses of many ways in which the internal emitter research bore on or had correlates to biomedical

mechanisms. Nevertheless, it cannot be said that the driving force was the understanding of basic mechanisms, to the extent seen in pure biochemistry, molecular biology, genetics, or even basic radiobiology using external radiation sources. This is not surprising. The inherent difficulties of handling radionuclides in biological systems are very large indeed. Frequently, it has seemed that much of physics, chemistry, and biology was involved in each major experiment, even the most practically oriented ones. Much attention had to be devoted to problems that, while sophisticated and completely necessary, could not reflect directly on the basic mechanisms underlying the observed phenomena.

A simple example is the gastrointestinal uptake of radionuclides. With the need to establish uptake figures for the most important radionuclides under a variety of conditions and in different species, as well as to determine even a single reliable figure for the many hundreds of elements of lesser importance, full attention could not be devoted to the mechanisms involved in gut uptake processes. This must be contrasted with the situations for iron and calcium, for example, where whole careers and major laboratories have concentrated on the mechanisms of their passage through the gut wall and other cellular barriers.

It is this author's view that we now are in a position to do much more purely mechanistic research in the radionuclide field. The major empirical answers are in. A good start has been made on explanations. To realize fully the enormous investment of the past decades, we should look even more for explanations.^(a) This is the true mission of scientific research and could, without doubt, open new vistas not yet appreciated.

It would be easy to urge extension of nearly all facets of the research described in this book. Unknowns remain in all of it. It could not be otherwise; for good research notoriously raises as many questions as it settles, or even more. Yet, in view of the limitations on resources now available, the shift in emphasis toward other areas (the needs are clearly great in chemical toxicology and quite justifiably require attention from some of the same investigators whose work we have been reviewing) and maturation of the field, it would be naive to recommend equal extension in all areas. Some priorities became apparent in preparation of a compendium like the present one. The author will expose a few of his conclusions regarding general avenues for continued work in the balance of this section.

a. Target Cells

The broad range of radiosensitivity of various cell types was worked out in considerable detail many years ago. But the classification applies mostly to the effects of high doses and high dose rates of external radiation. When we turn to low doses and low dose rates and add the complications of radionuclide metabolism, the picture becomes murky indeed. Over and over, attempts at

(a) A pertinent example concerns the influence of valence state. The work during World War II made a start toward determining the importance of valence state on processes such as gut uptake and pharmacokinetics. The chemists soon had far more information concerning oxidation states and the interrelated valence states that could be assimilated for the biomedical experiments. It is time to review much of the experimental work in a more sophisticated fashion (Durbin 1986b).

rigorous dosimetry and understanding of mechanisms came to grief because the true target cells were not known with any certainty. More work with this objective would assist with a wide range of problems.

b. Mechanisms of Carcinogenesis

It cannot be said that the work with radionuclides has contributed as much to developing basic ideas on carcinogenic mechanisms as research with external radiation sources. The problems with radionuclides introduce too many complications. Yet, cancer of organs such as bone or lung at low radiation doses is typically developed through the mediation of deposited radionuclides. We must keep on and find out in depth why certain radionuclides are much more carcinogenic than others and what role, if any, is played by cofactors of various types. The radionuclide field contains some puzzles worth solving in the area of carcinogenesis.

c. Uptake, Distribution, and Excretion—Species Comparisons

In this author's opinion, the enormous bank of information on these subjects needs little further expansion along the lines applied to date. A few notable exceptions reside in metabolic constants for compounds of the more esoteric elements and for behavior in environmental media. Some "constants" are still based on only one or two experiments, sometimes in a relevant species, sometimes not. Recent experience (e.g., with ^{237}Np) has revealed that an element can go from "esoteric" to one of considerable importance in long-term waste disposal on the strength of a substantial change in only one metabolic parameter. The metabolic models used for dosage calculations are slowly being reviewed. When examples of really shaky basic data turn up, the biomedical community should be prepared to provide better information.

Saying that we do not need more of the same is not to be construed as indicating we have all we need. As eloquently described by Durbin (1984, 1986a) and by Wrenn et al. (1985), even in the case of a much-studied element like uranium, we still have many needs. When sophisticated model-making is undertaken, the gaps in our knowledge become all too apparent. Inconsistencies made Wrenn et al. state, "no single model or combination of parameters . . . is completely consistent with the experimental data." Part of this results from uncontrolled variables. Some may never be controllable. However, future experimental work needs to be focused much more rigidly on the scientific hypothesis—in this case, the model being tested. The earlier work was more empirical, even range-finding. That is what we need little more of.

Another exception to the proposition that we are almost surfeited with plain distribution and excretion data lies at the micro level. While macrodistributions are well documented, much more needs to be found out about the behavior of many important radionuclides at the level of microdistribution. If we are eventually to be successful in identifying the true target cells, we will need much better information on microdistribution to accomplish meaningful dosimetry.

It will be realized, of course, that much of our information on uptake, distribution, and excretion is empirical. Complex retention functions have been derived and complex models built, but the exact meaning of the terms of such functions, indeed whether or not they have any physiological or biochemical meaning, is mostly postulate. Research that will do more than describe the behavior of radionuclides in living organisms, but place it in terms of specific

biomedical processes, has been pursued in some areas and with some success. However, much more of our future research in pharmacokinetics should have mechanistic postulates and mechanistic goals and be much less empirical. A few brilliant insights into what is actually going on could save thousands of hours of trial and error.

A persistent problem throughout the research on the pharmacokinetics of radionuclides has been the sometimes large species differences, even between common laboratory animals and between animals and humans. While one solution is to use only data from humans, this has always been difficult. The current phobias toward radioactivity make more such work nearly impossible, except under conditions of accidental exposure or through findings from the constituted registries. A much greater effort is needed to explain why the rabbit or rat may differ from the dog or primate, and when the explanation is found, to determine whether or not the processes responsible do or do not operate in humans. Throughout the preparation of this book, it has been surprising to find how little attention has been given to *explaining* obvious species differences. Good research in this area could have practical uses, but primarily it could help us understand the diversity of nature.

d. Pharmacokinetics in Humans

The need for interspecies comparisons discussed above underlines the need for gathering and utilizing all possible information in humans. Nuclear medicine will supply much information for relatively short half-lived materials. For the rest, a considerable burden is placed upon the few potential sources we have, such as the Transuranium and Uranium Registries, the continuing follow-up of exposed populations such as the Los Alamos workers, and the uranium miners, uranium mill workers, thorium plant workers, and a follow-through to the end of the radium dial painters, patients, and others receiving radium. In the event the future brings unexpected effects to the surface, we would require the best possible information to reconstruct the dose. We dare not muff the opportunity.

e. Epidemiology

If money were available to carry forward only one activity in addition to mechanistic work, this author would probably urge that it be put into sophisticated epidemiology. Measurement techniques are now improving to the point that much larger segments of the population can be assayed for their burden of radionuclides. Thus, much larger samples may be possible. Even failing this possibility, it should be recognized that many of the worker and other exposed populations are now entering the age group most likely to show previously latent long-term effects. The populations are sometimes small, but even so, they should not be allowed to scatter beyond retrieval. The recent entry of some of the uranium workers of World War II into an epidemiologic study is a very hopeful sign. Nevertheless, it must be remembered that many members of this group, as of the groups exposed to radium, can be expected to live into the twenty-first century and that as full and complete a follow-up as possible of them is still required to do a fine rather than just a good epidemiologic study. The same applies with equally long projected times to some of the other important radionuclides.

With emphasis turning more and more to the use of risk estimates for expressing potential health effects from radiation and other agents, the need becomes

still greater for a full-fledged follow-through on the groups now under study and any new ones that may arise. It may be tempting to turn off enterprises in areas where no obvious biological effects have appeared. Let us not forget that incontrovertible evidence of lack of effects in a study carried to its logical conclusion and correlated with good pharmacokinetics and dosimetry may be even more valuable than a shaky positive result.

A word of caution is needed, however. Recent years have provided the author an opportunity to mingle some with epidemiologists. He is inclined to the view that few if any populations in the real world meet the rigid criteria of epidemiologic suitability. Thus, it is possible that none of the precious groups we have taken so seriously would pass muster as first-class epidemiology candidates, though some might come close. Therefore, on pragmatic grounds, we might be wise to continue work in several areas, not just in epidemiology.

f. External Versus Internal Sources—More Microdosimetry

There is no doubt that the complexities of internal dosimetry make comparison of doses from deposited radionuclides to those from an external source quite complex. There has been a general tendency to consider that a rad is a rad regardless of source. This is axiomatic, but cannot be proven until actual measurements are made of the absorbed dose at the relevant target. This has yet to be done. We need instrumentation and methods to do it.

Meanwhile, we are relegated to calculations based upon broad assumptions that by and large by-pass the refinements of microdosimetry. While it is true that the work generated by the "hot particle" controversy has repeatedly indicated that average dose is the most relevant parameter, this is on a gross scale. Microdosimetric approaches for tissues like bone and lung are still in need of a unified approach and a serious effort to determine how much difference it makes whether the energy is delivered at short range by a deposited radionuclide or absorbed from the passage of photons from a relatively distant external source. The reported extra effectiveness of Auger electrons produced in situ is a case in point, as is the difference in effectiveness among the iodine isotopes.

This work may be regarded by some as excessively academic in contrast to some of our other needs. Nevertheless, we cannot separate any observed differences between external and internal sources and among internal sources as being due to differences in localization of the radionuclide, in specific activity, etc., or aspects that may reside in microdosimetry without a more overt attack.

g. Risk Estimates

Present trends make careful derivation of estimates of risk necessary for all of the important radionuclides. A desirable format is the toxicologic approach, viz., direct determination of risk in relation to intake in humans without the intermediary of a radiation dosage calculation. The number of radioelements that give promise of being handled in this way is unfortunately very small, e.g., ^{226}Ra , ^{224}Ra , radon and daughters, thorium isotopes as in Thorotrast, perhaps someday plutonium. Direct estimation of risk through animal experiments may be possible in some cases but has the problem of species differences.

Surprisingly, even with our most extensively studied radionuclide in humans, ^{226}Ra , it has turned out not to be easy to derive a consistent set of risk factors directly from intake or body burden. It is urged that all current and future data

(e.g., from epidemiologic studies, from the Registries, etc.) be gathered and analyzed with a view toward reliable estimates of risk. This includes the all-important follow-through of the radium cases. The external radiation field has been far ahead, but is now stalled by the problems of dosimetry in the Japanese. It is time for an overt effort to help the radionuclide field catch up.

h. Genetic Effects

Throughout the book, it has been apparent that few radionuclides deposit selectively in gonadal tissue. The few cases extant are somewhat isolated and have not been confirmed. Partly for this reason, direct determination of genetic effects in mammals in the manner of the "megamouse" experiment for external radiation was by-passed for decades. Only recently have serious attempts been made to check out the relative effectiveness of internal emitters compared to external radiation in producing genetic effects in mammals. The results to date do not indicate that many big surprises are lurking around the corner. Yet the effort has been small. While no huge expansion is advocated, continuation of work in progress to its logical conclusion and a sufficient checking out to be sure there really will be no surprises are recommended.^(a)

2. Unfinished Business—Chapter by Chapter, Subject by Subject

In addition to the general indications for work yet to be done described in the previous section, a very brief review according to the subject matter of the chapters may provide needed further summary and emphasis. These are in addition to the points made in section 1 above.

Chapter 1—Radium

The Massachusetts Institute of Technology (MIT) radium studies indicated a leveling off of bone cancer incidence in humans at about 30% on a cumulative incidence scale of 100%. The Argonne radium studies and the current analyses by the Center for Human Radiobiology do not show such a clear-cut maximum. It is hoped that the further follow-up of the ^{226}Ra , ^{228}Ra cases will keep this phenomenon in view for further checking. It may have as much input on mechanisms as further agonizing over the shape of the dose-response relationship at low doses.

While the populations are perhaps not epidemiologically as suitable as might be wished, those exposed in areas of the country using water with high natural radium content should not be forgotten.

The mechanisms of two phenomena seen in the animal work with radium have had only partial explanations. Working them out would be of interest, though not of high priority. The first, generation of eye lesions, may be limited to the dog and not be of much practical import to humans. The second, generation of blood-vessel calcification, does not seem to be species-limited and is unique to radium. The mechanism remains cloudy. Why only radium?

(a) Recently, the potential for genetic effects from deposited radionuclides has been reviewed by authors in the USSR (Lyaginskaya et al. 1985). They conclude that the current ICRP limit for nonstochastic effects (0.5 Sv) is not sufficiently conservative for potential genetic effects of some important radionuclides, including plutonium. This may augur for a more intensive effort than is implied above. It is also recommended that the interested reader consult the recently-issued NCRP report on genetic effects of internal emitters (NCRP 1987).

The true risk of carcinoma of soft tissues from radium is not well established. While there is no doubt of the phenomenon, the current data on incidence indicate that it may be a very late effect. The risk figures derived from early experimental data may need revision as work progresses. Also, a greater incidence of soft-tissue cancers seems to occur with ^{224}Ra than with ^{226}Ra . This should be checked out by completion of observations in animal experiments and the exposed human populations.

Finally, early work showed that the retention of radium increased with increasing dose level in all species. The mechanism of this effect should be worked out, since it might have some general implications.

Chapter 2—Uranium

It is hard to believe that after the herculean effort on uranium during the years of World War II and the smaller-scale continuation in the decades since that there is any further work needed. Yet, there are two major dilemmas regarding uranium that persist.

Despite all the work, there seems to be a persistent quandary on whether or not to base standards for exposure to natural uranium on potential radiation effects or potential chemical toxicity (chapter 16). We saw in chapter 2 that heroic measures were needed to deposit enough insoluble natural uranium in animal lungs and for long enough to produce clear-cut evidence of radiation effects. So far as this author is aware, this is still the only documented case of radiation damage produced by natural uranium, except for some implantations of the metal. It never was possible to induce bone cancer. All of this was at very high concentrations. Nevertheless, those proposing standards for drinking water, where it is the soluble, potentially nephrotoxic forms that are important, keep reiterating an intention to use the potential radiation dose as the criterion. There is no new evidence to support this. Indeed, we have new evidence that chronic uranyl nitrate injection in the dog at moderate doses can produce a chronic uremia syndrome (Fukuda and Kopple 1980). Use of the inhalation route did not change things. Using both soluble and less-soluble forms of "yellow-cake," Eidson (1981) at Lovelace found the only site of extensive damage to be the kidneys. Goldman (1981) has stated categorically that "uranium toxicity in drinking water should be based on chemical toxicity and not radiation toxicity." It would seem that a small but conscientious effort could resolve this nagging "dilemma," since it seems hardly to be a dilemma at all.

The second outstanding dilemma with uranium is the lack of correlation between measured amounts of uranium in autopsy and other tissue samples and that predicted from air sampling data. This was discussed in the appropriate chapters but is reiterated here. The accumulating information from the Uranium Registry should help, but it must be accompanied by a much more serious effort to gather, analyze, and evaluate the exposure data. If the whole dilemma is based upon the nature of the sampling and characterization of the workers' exposures, we should be clever enough to find out once and for all. These problems are expanded upon further by Stannard (1984, 1986). Occupational exposures to uranium are not stopping.

As a corollary to the above areas, it should be noted that recent data gathered by Morrow and colleagues at Rochester (Morrow et al. 1982) indicate that the threshold level for nephrotoxicity of uranium in the kidney may be lower than that commonly employed. This, too, needs cognizance in future work. Also, Morrow et al. indicate that the development of tolerance is not a simple or

even a general phenomenon. It is definite when the measure is mortality. It is not so definite by other measures. Finally, this new work shows evidence of effects in many parts of the kidney, not just the proximal convoluted tubule, as considered dogma for many years (chapter 2). The effects are, however, more subtle and perhaps require more chronic exposure or higher concentrations. All of this makes it clear that the uranium saga is far from finished. The recent survey of uranium models by Durbin (1984 and 1986a) attests to this. Also see Wrenn et al. (1985).

In chapter 2, we bemoaned the lack of extended effort beyond the work of the war years, and shortly thereafter, on the higher-specific-activity isotopes of uranium. It appears that there is now little need for further urging. Ballou and colleagues at Battelle have mounted a continuing study of uranium-thorium breeder fuels and are already publishing on the metabolism and long-term effects of ^{233}U - ^{232}U -oxide and nitrate fuel materials (Ballou et al. 1985; Ballou, Case, and Haggard 1984).

Chapter 3—Radon and the Uranium Miners, Radon in Dwellings

The designation of the true target cells, further examination of species differences, and the logical conclusion of the epidemiology already mentioned apply especially to research in this area. In addition, it would be desirable to have much more and better dose-response relationships for the uranium and other miners, and a resolution of the true role of cigarette smoking and of other contributing factors. The present circumstances of lower exposures and fewer miners, while good for the total health status of that population, make it somewhat unlikely that we can expect large expansion of the dose-response data for humans. But we should keep trying. More conclusive evidence of the role of contributing factors is needed via further animal experiments. It would be desirable if these were made part of a coordinated attack on the mechanisms of carcinogenesis rather than done in isolation.

The role of unattached daughter products is much less well understood than it should be.

The recently developed concern about population exposures to radon and daughters in energy-efficient, "tight," buildings has created such a stir that the need for further work needs little urging here. It must be realized that only a minuscule fraction of dwellings or other subject buildings in the United States have been surveyed. Perhaps a more realistic sample is needed to make us more confident about the dimensions of the hazard. This is hardly research that could be put in the same category as understanding the mechanisms of action of radon daughters, but it requires doing. A bit more action is needed, too, on remedial measures. This may be more in the nature of providing information and advice than in performing new research. A concise and very useful general summary of the problems of environmental radon has been published very recently by scientists at the U.S. Environmental Protection Agency (EPA) (Cothorn and Smith 1987).

The need to be alert to opportunities to study populations around the spas was emphasized in chapter 3.

Chapter 4—Polonium and Thorium

While there are many unsolved problems with polonium, most of them are generic and do not require special mention here. Unfinished business with thorium concerns largely completion of the studies with the Thorotrast patients,

a final determination of the role, if any, of chemical toxicity in the action of Thorotrast, and a thorough epidemiologic study of the thorium industry workers.

Chapter 5—Early Days of Manmade Radioisotopes

Unfinished business from these days will be considered in connection with later chapters.

Chapter 6—Wartime Work with the Fission Products

Carry-overs from this work were taken up in chapter 8.

Chapter 7—Wartime Work with the Actinides

Ditto. The expressed need for more cellular-level work was only partly met in the postwar work described in chapter 8.

Chapter 8—Postwar Work with the Fission Products and Actinides

There have to be questions on the future status of the several large experiments begun in the early postwar years and described in some detail in chapters 8, 9, and 13. Briefly, they are nearing their original goals. Some have a few animals remaining. All require more data analysis and preparation of publications, as well as final reports. Furthermore, the results of the several efforts should be coordinated to be sure there are no hidden inconsistencies. Obviously, many leads toward mechanisms were uncovered during the work. These should not be lost sight of (Evans 1983). A good example is seen in a paper by Stover (1972) based on the Utah experiments. There is a formal list of unanswered questions and future research needs. These leads should be assembled now for the benefit of posterity and decisions made on how to follow them through.

Opportunity was taken in 1983 to formally review the life-span effects studies in animals. This was on the occasion of the twenty-second Hanford Life Sciences symposium held September 27-29, 1983, under the ambitious title, "Life-Span Radiation Effect Studies in Animals: What Can They Tell Us?" The agenda included both the long-term experiments with radioisotopes, many of them reviewed herein, and those with external radiation. Nearly all of the U.S. work was reviewed as well as many Western European studies. Unfortunately, there was no real summary of efforts in the Soviet Union. The meeting went for a full three days, and such a volume of complex work was presented that it has only recently been published (Thompson and Mahaffey 1986).

The general reactions were upbeat. These are difficult, expensive, and time-consuming experiments. Yet, I found no investigators who wished they had put their energies elsewhere.

It was clear that the studies had done much more in many instances than was originally expected. In the case, for example, of the several beagle experiments designed originally to check out the relative toxicity of several bone seekers,^(a) much was learned about the basic physiology and toxicology of bone and of the respiratory, lymphatic, and other systems and of carcinogenesis.

The long-term inhalation toxicology experiments (chapter 9) were pioneering efforts that taught us much about the respiratory system and its potential for developing cancer. Very little of the information could have been learned without the experiments.

(a) It is not the fault of the experimenters or experimental design that the relative toxicity figures in the dog were not greatly different from those derived earlier from rodent experiments. Let us be thankful that at least one major dilemma was put to rest. The species were more alike than different.

As alluded to above, information on mechanisms or paths that might be followed in the future toward understanding mechanisms were unearthed. Let it be reiterated that it is the follow-up of mechanisms underlying the phenomena brought to light by these tremendous efforts that is the prime unfinished business from these experiments. Nevertheless, despite the relatively high cost, inflation, and budget problems, the original protocols cannot be markedly truncated without serious diminution of the total yield. It is urged that a national effort be mounted to screen carefully the pros and cons of future work to avoid regrettable mistakes.

Recently, Thompson (in press) presented a short summary of the several large beagle experiments with radionuclides done under the auspices of AEC and its successor organizations, the Energy Research and Development Administration (ERDA) and the Department of Energy (DOE). This is part of a systematic review being done for the Department of Energy. The complete manuscript is awaited eagerly. Only with this in hand can a full and balanced evaluation be made of what, and how much, unfinished business we have before us or should have before us as a result of these life-span radiation effects studies. This is important despite the fact that the efforts have already netted us a position of relative strength considering the reluctance with which nature gives up her secrets.

With the growing awareness of the tremendous job ahead of us in chemical toxicology, it is tempting to suggest that the organizations that have done such a superb job in radiation toxicology simply transfer to this new objective. The shift in subject matter might be difficult for some personnel, and details of the techniques would be different. Yet is this not more efficient than organizing new laboratories?

The shift is already under way in some quarters. The opportunity should not be lost because of possible differences in sponsoring agencies or other administrative complexities. Meanwhile, the organizations should be urged to summarize and publish all facets of their operations with radionuclides and make proposals bearing on mechanisms. As stated in section a. on page 1830, we still cannot explain why one radionuclide appears to be much more carcinogenic than another without obviously different gross pharmacokinetics.

Chapter 9—Inhalation Problems—Radioactive Dusts and Particles

At the end of chapter 9, an excerpt was given of a planning document produced in 1975 by the Division of Biological and Environmental Research of the then-new ERDA. This is reproduced again below for the convenience of the reader

The declaration by Congress on October 8, 1974, to accelerate development of all energy sources to meet the needs of present and future generations, and to make the nation self-sufficient in energy, also directed that public health and safety be concomitantly assured. The generation of new toxic aerosols by rapidly developing energy sources, superposed upon those agents presently responsible for an alarming increase in lung cancer in the general population and severely increased chronic respiratory disease in industry, could rapidly magnify the danger of wide-spread disease caused by inhaled airborne contaminants. This will occur unless a comprehensive program is promptly implemented to define the nature, properties, environmental levels, and biological disposition of these airborne toxicants, as well as mechanisms of pulmonary or systematic disease caused by aerosolization of energy-related materials. Such a program must incorporate 1) identification of inhalation hazards and characterization of their sources, 2) studies of physical-chemical characteristics of air-borne particulates and gases that affect

their physical and biological behavior, 3) evaluation of factors and processes that affect respiratory tract deposition and retention, 4) increased understanding of mechanisms, pathways, and kinetics of biological disposition of deposited agents, including cell-mediated and dissolutive clearance, translocation rates and fractions, and processes of elimination or detoxification, 5) identification of the nature and degree of deleterious effects, both acute and delayed, resulting from inhalation of toxic materials arising from, or related to nascent energy technologies, 6) establishment of primary and sequential dose-effect relationships, 7) identification of sensitive populations and studies of the influence of age or compounding diseases upon effects, 8) predictive models based upon experimental work, 9) evaluation of effects of localized concentrations versus diffuse distributions of inhaled contaminants in critical tissues, 10) mechanisms of repair and recovery.
(ERDA, DBER 1975)

Progress has been made, but much remains to be done. The true explanation for the unique carcinogenic effectiveness of some radionuclides in lung, for the lack of carcinogenesis in general in pulmonary lymph nodes, and the many problems of the respiratory system outlined earlier remain for the future.

Chapter 10—Inhaled Gases

Unfinished business with the noble gases, tritium, iodine, and related entities resides mostly at the cellular level and is mechanistic. The reason that a transmutation effect should appear with tritium only when the labeling occupies very specific sites is not known. Nor is the dosimetry of some of these very low-energy beta emitters very well understood. It appears unlikely that the general problems raised by these considerations will be neglected so long as molecular biology continues in its state of eminence, but it will require also the special touch of the trained radiobiologist.

Chapters 11 through 15—The Environment Chapters

The unfinished business regarding environmental aspects of the transport and effects of radionuclides is taken up in more than usual detail in each chapter. A few generalizations remain to be made. The vastness of the world environment and of the biosphere make it likely that we have more unfinished business here than in any other aspect of the radionuclide field. Unfortunately, ways to get firm answers are not clear; certainly not easy. They are complex, expensive of manpower and money, and international in scope. Also, they are strongly interwoven with our general environmental problems, since the ecosystem is responding to all stimuli simultaneously. With the decrease in levels of worldwide fallout and strict controls on nuclear installations, it must be said that the problems of the environment from radioactivity may be less pressing than many others, e.g., pesticides for agriculture, industrial pollution, and smog.^(a) Yet, the relative ease of measuring the movement of radionuclides, the tremendous start we have in radioecology, and the needs to understand mechanisms foster continuing research in the field.

(a) This was written before the Chernobyl incident and the special addition to this chapter on that subject. There will, no doubt, be a recrudescence of research on the passage of radionuclides through the environment. Nevertheless, it can still be said that we have a better grasp of what needs to be done than in the case of chemical contaminants, and are relatively further advanced.

Among the reasons for continued effort are the following:

1. It was clear from chapters 11 and 12 that the ecosystem approach to assaying possible effects of small increments in radioactivity presents a formidable challenge. No clear-cut changes have yet been seen except in localized areas. We are inclined to concentrate on man and to avoid a frontal ecosystem approach. Present indications are that the potential problems from present levels of radioactive contamination are small. Yet, the experts are at work and aware of the possibilities for surprises. Even though they seem unlikely at present, vigilance should not be relaxed.
2. Consideration of the environment has focused attention on population in contrast to occupational exposures. This means a much broader base is needed in terms of the characteristics of "reference man," the validity of the critical pathway and critical population concepts, and a much more organized approach to the effects of disease states and physiological variables. We have a good start, but much more is needed.
3. In the reconstruction of the doses from fallout around the Nevada Test Site, many ingenious approaches have been taken, as well as a prodigious effort at sifting through mountains of data. Much of this remains in special archives that may be lost when the current pressures from litigation ease. It is urged that documentation in a permanent, relatively concise form be considered and current activities be carried as far as they usefully can.
4. The researches stimulated by the problems of fallout uncovered important biological facts and made very respectable progress in understanding mechanisms. Examples are the presence, magnitude, and explanation for discrimination factors and also of concentration factors; the importance of soil chemistry and physics; and much new information on plants and their role. Yet the story is incomplete. Some of the concentration factors, for example, are based upon only incidental findings and may be confined to only one or two observations. Radioecologists are aware of these needs but may need further encouragement.
5. Obviously, the problems of long-term waste disposal command much attention. Low-level radioactive waste seems, to this author at least, to be more a problem of human cursedness and political considerations than bona fide technical issues. However, the problems of environmental transport from currently active medium- to high-level waste disposal sites require further scientific attention. The choice of eventual new repositories now seems less a technical problem than it did a few years ago.
6. Turning to environmental transport, in general, not just waste disposal problems, we must return to chapter 15. The complex and sophisticated models for environmental transport of radionuclides have far too many "default" values. Before these get embodied into established procedures and their tentative nature forgotten, the biomedical community should be able to supply many more carefully measured and reliable figures.

Chapter 16—Internal Emitter Research and Standard Setting

In addition to the need for strengthening some of the metabolic constants used for computation, already mentioned, there is much unfinished business in the validation of our current standards. As the several epidemiologic enterprises bring in further information, their bearing on the validity of the standards derived earlier should be kept constantly in mind. Furthermore, the need for valid risk estimates requires considerable attention, as was described earlier.

The atmosphere of contention and litigation currently upon us cannot help but produce further challenges to the adequacy of radiation protection standards. The fact that some of the input data were sparse and crude in the early days should not be allowed to cast doubt upon a system that has been, on the whole, adequate, and in many areas, superior. Let us gather and introduce better metabolic data where needed. Conversely, let us waste no more time on empirical approaches to finding effects at the very low doses associated with the standards. Learning the intricate mechanisms of radiation effects at low doses presents greater promise for both external radiation sources and deposited radionuclides.

Bioassay, by either excreta analysis or whole-body counting has been alluded to in many connections, e.g., excretion kinetics worked out during the war years (chapters 6 and 7); postwar expansions and modifications of these (chapter 8), and some brief references to determining body or organ burden in chapter 16. We have not expanded upon the subject since it was more a regulatory and assessment enterprise than research, even though the basic information was derived from the research activities. One of the problems has been that the instrumentation and methodology were frequently strained to or below their detection thresholds. Also, variability was great at the low levels associated with allowable or below organ or body contents. Recently, several ultrasensitive methods for radionuclides of interest for bioassay have been developed. These include instruments well beyond the types described in chapters 17 and 18. The potential of these for bioassay procedures is important for the future. The need for bioassay will not go away.

Chapters 17 and 18—Instrumentation and Methodology

Despite increasing sophistication and miniaturization of instruments, it appears that further improvements in reliability are still needed.

One need that this author intended to stress appears to have been met recently. This is the need for a survey instrument with a range of several orders of magnitude that would not saturate in a strong radiation field and give false negative results, yet be sensitive at fractions of the maximum permissible concentrations. Such an instrument is now available. There are probably many other needs that the instrument makers are hard at work on.

It appears likely that the enormous demands made by nuclear medicine on the instrument makers will ensure continued progress in measurement of radioactivity, but we should not depend too much on the needs of nuclear medicine. We have our own needs.

Chapter 19—Therapeutic Procedures for Deposited Radionuclides

The outlook for therapy would be greatly enhanced if agents or procedures were found that could pry loose radionuclides that have become "fixed" in the tissues. At present, we are handicapped by the need for prompt action, even before it is clear whether or not therapeutic removal is indicated. However, the prospects for such a major breakthrough are slim. We are flying in the face of basic phenomena of biochemistry where any effective agent might well disrupt as many normal bonds and complexes as it did the abnormal, "foreign," objects. Yet, the need must be cited and kept in mind for future reference.

It was obvious in chapter 19 that much more could be done on the basic pharmacokinetics of chelating agents and in the synthesis of new compounds. It is likely that this enterprise is well in hand in the cognizant laboratories,

primarily those abroad, without a special reminder here.^(a) The search must include not only better agents with higher therapeutic ratios, but special attention to the embryo and fetus, if present; the effects of age; and, especially, the influence of underlying disease processes.

A corollary to such developmental work is the need to maintain a corps of physicians and radiation protection experts that can respond quickly to unexpected contaminating events and make early estimates of the potential need for therapy.

Finally, as urged at the conclusion of chapter 19, we need to become better prepared for instances of population exposure to radionuclides, in addition to the more conventional occupational event.

Chapter 20—Selected Aspects of Nuclear Medicine and Tracer Chemistry

The broad front of activities in nuclear medicine is almost certain to encompass any ordinary unfinished business made apparent in the chapter. The objectives of the clinician, of the investigator interested in the behavior and effects of radionuclides, and of the radiation protectionist are essentially concurrent in this field. Toward the end of chapter 20, promises for a possible new era were mentioned. There was envisaged a recrudescence of therapeutic uses as well as continuation of the enormously useful diagnostic modalities. Tentative forays into new areas such as monoclonal antibodies, in-situ production of therapeutically useful radiation doses from neutron interactions with stable isotopes, and others were mentioned. The talents now available combined with methodologic breakthroughs may be able to reverse the discouraging experiences with radionuclides for therapy encountered in the middle to late-middle decades of this century. The basic idea of placing a significant dose in a significant area by means of a radionuclide attached to a suitable carrier is worth further exploration.

IV. Further Commentary—Chernobyl

A. Background and Need for Discussion^(b)

The manuscript for this book was completed when the nuclear reactor accident at Chernobyl in the Soviet Union occurred. The author and sponsors thought this major event involving exposure of a population to the fission products from a nuclear power reactor required specific comment as part of this final chapter. In accord with the plan of the chapter, we will look at both retrospective and prospective aspects. Did the years of research and field work described in part in this book make the task of reacting to this major emergency easier and surer?

(a) The U.S. effort has been drastically curtailed by budget cuts.

(b) This author's initial review of the facts about Chernobyl was greatly facilitated by W. J. Bair by provision of data from the International Atomic Energy Agency (IAEA) meeting (1986), a lecture by Marvin Goldman to the San Diego chapter of the Health Physics Society, a prepublication copy of Dr. Merrill Eisenbud's review for the third edition of his classical text (Eisenbud 1986), and references contained in those documents. Also, two World Health Organization documents (WHO 1986a,b) have been noted. Details have been inserted in the references. Later, Dr. Bair chaired an interlaboratory task group sponsored by the Office of Health and Environmental Research, Office of Energy Research, DOE, which issued a report in June 1987 (DOE 1987). The year 1987 also saw numerous open literature publications, some of which have been added to the prepared text if needed.

Did the knowledge gained, in the decades of biomedical work we have discussed aid in making projections of future potential effects? If so, to what extent? Did the accident expose serious gaps in our knowledge, and if so, what? Were there any surprises, major or minor, i.e., events not predicted by the body of knowledge at hand? Is new research required to assist future generations?

Finally, it seemed that the reader might appreciate a brief listing of chapters in the book that bear significantly, in historical context, on the problems of Chernobyl.

B. The Event

The event itself has received such wide coverage that no need is apparent to repeat a description in detail here. Suffice it to say that we are referring to the accident in Unit 4 at the Chernobyl power station on the Pripjat River about 90 km north of Kiev, one of the USSR's largest cities, and close to the town of Pripjat, population about 45,000. It occurred in April 1986. The reactor was destroyed following a set of operations that went far beyond normal procedures. The resultant steam explosion and fire released about 50 MCi of fission products in particulate form and another 50 MCi or so of radioactive noble gases such as radioxenon, radiokrypton, radioargon, etc. (IAEA 1986). It is stated that about one-fifth of the total iodine inventory was released, about 12% of the cesium, and a few percent of the other normally nonvolatile radionuclides.

The biomedical problems involved exposure to ionizing radiation doses from the radioactive materials in the cloud; heavy contamination of skin and clothing; trauma and burns to those directly involved in the accident and fighting the fires; external doses from fission products deposited on objects and on the ground; and actual plus potential radiation doses to internal body organs through uptake through the skin, and by inhalation or ingestion of radioactive materials of many kinds. Not all of these problems applied to all persons involved, obviously. The close-in doses, particularly from the cloud passage, could be very high, while those from the cloud at considerable distances could be considerably lower. All of the external doses decrease fairly rapidly as a power function of time. Except for workers and fire fighters with gross contamination of skin and/or inhaling highly contaminated air, the problems from radionuclides deposited in internal organs would be (and were) less acute but longer lasting. The intakes might even increase with time because of recycling in the environment (chapter 15) and possible solubilization of the contaminants over time. The environmental contamination aspects will require a considerable period to unravel.

The Soviet report (IAEA 1986) describes the radiological considerations in three categories: (1) on-site, (2) areas within 30 km, and (3) in European portions of the Soviet Union. Others have described radiological measurements in European countries outside the Soviet Union and the measurable but biologically unimportant contamination from vestiges of the plume in North America and Asia. Obviously, these divisions correspond only roughly to the degree of contamination due to the absence or presence of precipitation, variations in wind patterns, and other meteorological factors that could produce large differences in local depositions.

As pointed out in detail by others, the graphite-moderated Soviet reactor design has few counterparts in other countries. The British reactor at Windscale is graphite moderated, as is the "N" reactor at Hanford in Washington State and

other old reactors, many of which are now retired; however, there are major differences. The accident at Windscale, described in some detail in chapter 11, might be considered a small-scale prelude to Chernobyl. However, the graphite fire was limited, the reactor was not destroyed, there was no explosion, and the releases involved primarily the most volatile fission products, e.g., ^{131}I and the noble gases, along with much smaller amounts of ^{137}Cs and radiostrontium. The totals were in the thousands of curies, not megacuries.

The magnitude of the releases from Chernobyl did not approach the total of releases of fission products to the atmosphere from weapons testing. However, some local deposits in the USSR are said to exceed the total deposition measured in that area from all of the weapons tests (Eisenbud 1986; IAEA 1986).

There is no doubt that Chernobyl was a major event, by far the most costly accident to a nuclear reactor in history in terms of both lives and money. Further details from the point of view of a physicist can be seen in Wilson (1987).

C. Was Our Knowledge Sufficient to Cope with the Sequence of Events?

In broad terms the answer is positive.

Physical events at the reactor were, sadly, largely predictable. The motivation for the removal of one safety measure, or device, after another is beyond our scope, and not predictable. However, the physical events, knowing the characteristics of these particular graphite-moderated reactors,^(a) cannot be said to have gone beyond the knowledge of those most versed in their characteristics and behavior. Other nuclear accidents have been attributed, in part, to failure of specific parts or systems to operate as-designed. This cannot be said of Chernobyl, except for a few small details.

The huge investment of time and effort in depicting the acute radiation syndrome by experimental work in the laboratory, field tests in the weapons-testing program, experience with the Japanese bombings, and the few accidents involving criticality or medical mistakes, made prediction of, and reaction to, the acute effects reasonably certain. They were complicated, however, by skin contamination, radionuclide intake, and in some cases, trauma.

The same body of knowledge, with the addition of information from partial body radiation for cancer therapy and other maladies in humans and animals, contributed to understanding what to expect in terms of subacute and long-term effects.

The estimates of risk, developed primarily from studies of external radiation sources, but modified by other studies including intake of radionuclides and application of the linear no-threshold dose-response relationship chosen for standard setting (chapter 16), made prediction of long-term effects possible. It is true that predictions of the total number of cancers to expect in the exposed populations have varied rather widely, especially in the earlier period after the accident, but these variations reside more in the degree of conservatism utilized by the predictors than in uncertainties in the risk factors

(a) For example, a positive void coefficient, a unique property of the RBMK reactor design, not present in Western counterparts.

themselves. Nevertheless, quantitative prediction of truly long-term effects in heterogeneous populations must be considered as one of the weaker points in the application of current knowledge. We need more, including the continuation to their logical conclusion of the epidemiologic studies now under way in the external radiation field, and with deposited radionuclides and the revision of the dosimetry of the Japanese bombings.

The experience with tracking and measuring fallout from nuclear weapons tests made tracking the plume from the accident almost routine. Whether or not the total biomedical toll of the weapons tests is considered to overwhelm the advantages of having this knowledge, it can be said that we did know how to track the plume and its associated fallout. Details can be found in chapter 12.

The constant surveillance of the environments around nuclear reactors throughout Europe gave the first alert that something was amiss. Many very early measurements were done at nuclear energy installations, while more extensive forces were being assembled.

The considerable experience with behavior of fission products in organisms and in the environment had already given reasonable approximations to use for calculating uptake from lung or gut, subsequent tissue distribution, retention and excretion kinetics, and thus potential dose hazard. Factors for environmental transport are also numerous and well-documented. However, the complexities of the environment and the usually low levels of radioactive contamination of it make for somewhat greater uncertainty in predicting long-term behavior and effects.

Contamination of food and water were thought of immediately, and rather prompt measurements of milk, for example, were instituted. This was important for iodine isotopes appeared very early in large quantities. Subsequently meat was sequestered and some cattle butchered before accumulations of radioactivity reached unacceptable levels. Literally thousands of laboratories could be recruited with instrumentation and techniques developed for the routine monitoring of food, water, and the environment. Most of this preparedness comes from the type of work described in the environment chapters, e.g., chapters 11, 12, and 15, and parallel work done in the Soviet Union.

The behavior of radioiodine was well established by work in both the environment and in medicine. Indeed, much of what we needed to know was depicted in the experiments, described in chapters 8 and 10, even as early as the Hanford biology symposium on radioiodine held in 1963 (chapter 8).

The effects of soil type on the movement of radionuclides into plants, especially the anomalous behavior of cesium, were known from previous work with fallout, in the USSR, in the Caribbean (Jamaica), and in experimental work in the field and in various laboratories (chapters 12, 13, and 15).

Possible prevention of radioiodine uptake in the thyroid was begun very early in the on-site population by giving stable iodine. This was based solidly on earlier experimental work and much planning in medical and administrative circles concerned with reactor safety. The promptness of the administrations demonstrated well the lessons learned fully for all prevention and therapy for radiation effects, viz., time cannot be wasted (chapter 19).

The special problems of residents of the arctic and subarctic regions where a very short food chain exists (lichen-reindeer-humans) are serious, if not catastrophic to their way of life. Nevertheless, the phenomena are reasonable extrapolations of information gathered earlier in connection with fallout (chapter 15).

We have a reasonable hold on the extent to which we can generalize from one element to another, and the limits to which application of the generality "mixed fission products" can extend. We know it is best to handle each element, even each chemical form, as an entity, where possible. But we know this is not practical and can fall back on generalized behavior of groups of elements, or critical elements, as worked out for weapons fallout (chapter 12) and research growing from the field tests (chapters 13 and 14). We do not know very well how much error may be introduced by selection of critical radionuclides, critical pathways, or critical populations. We can be assured, however, that such selections will have to enter to some degree.

Obviously, we have learned fully that it is not enough to protect against, or calculate, the dose from cloud passage alone. We saw at Chernobyl no repetition of the neglect of internal dose that characterized the thinking around the early weapons tests and early estimates of reactor accident consequences (chapters 11, 12, and 15).

Relatively sophisticated and rapid computer programs are available for calculation of both external and internal dose. These will suffice for "ballpark" figures. More detail is needed, however, for specific sites and exposures.

Finally, we can feel reasonably assured that no unexpectedly devastating effect will occur in the environment, except possibly locally, as a result of the accident. This comes from careful environmental work, still in progress and needing extensions.

Let it not be concluded that we had all the knowledge that might have been desired. Only the future can tell how well our present knowledge has really served us. It is hard to imagine, however, what our situation might have been had the enormous efforts in radiation biology, radioecology, and toxicology, plus the adventitious contributions from radiology and nuclear medicine (chapter 20) not been supported and pursued with enthusiasm as described in part in this book.

D. Any Surprises?

Obviously, a major event like Chernobyl would be expected to reveal surprises and point up gaps in our knowledge. Let us look first at the category of surprises.

To some, the greatest surprise surrounded the circumstances of the event (Eisenbud 1986). Human error has underlain other reactor accidents, including Three-Mile Island and some of the large chemical releases of recent years. As the Soviets described (IAEA 1986), many of the steps taken by the operators before the explosion were unauthorized, and thus, technically "errors." However, the basic design of the reactor (positive void coefficient) was a very important ingredient in the response, and this was not only well-known but is not a characteristic of most other designs of graphite-moderated reactors. Thus, in retrospect, the fact that the event took place cannot be regarded as a genuine surprise.

The release of substantial amounts of the inventory of fission products was no surprise. Yet, in view of the high temperatures and extent of involvement of the reactor core, the fact that the estimated release was calculated as only about 3.5% of the reactor inventory is somewhat surprising. The relatively small release of strontium isotopes and of actinides accounts in part for this fact, and is probably to be viewed as at least generally unexpected, if not surprising, to the

experts.^(a) There was little need at Chernobyl for our storehouse of knowledge about the bone seekers (chapters 8 and 13).

In the context of the early studies, the role of cesium was, perhaps, of even greater significance than expected. We learned from experience with the long-term contamination of the Marshall Islands and Nevada Test Site that cesium could assume a dominant long-term role, even with weapons fallout. Reactor discharges confirmed the idea. Nevertheless, the concentration of the longer-term biomedical problems on cesium and related elements was not fully predictable. In contrast, the role of the radioiodine was classic both qualitatively and quantitatively.

It is too early to hazard more than a guess as to whether or not there will be surprises in the biomedical area. The early effects were more or less classic. Only as the longer-term effects unfold can we compare biological effects with predictions.^(b)

The same applies to experiencing surprises in the area of environmental transfer. However, the potential for many surprises in this area seems large. The data base for the computer models is quite idealized and generalized (chapter 15). It may or may not fit the circumstances of Chernobyl or the environment of northern Europe.

E. Gaps in Our Knowledge and Need for Further Work

We will consider primarily the biomedical areas, first looking back and then looking ahead to future needs.

Probably the most obvious gap in the biomedical area concerns cesium. As described in detail in chapters 8, 10, 12, and 13, we concentrated our experimental work, for good reasons, on external radiation, the bone seekers, and on iodine for serious examination of long-term biological effects. Long-term, low-level experiments with cesium isotopes were not done, although there were fairly extensive experiments at ANL, at Lovelace Inhalation Toxicology Research Institute, in the USSR, and elsewhere at moderate to high levels of cesium. Whether or not we are safe in assuming (as was done) that, because of its more or less uniform tissue distribution, the cesium effects will imitate those of prolonged whole-body external radiation at low levels, can now only be speculated. It would be comforting if cesium had been inserted in one of the "king-sized" experiments (chapter 8). Mounting of a full-scale experiment now is of doubtful value, however, since the information may be coming in from the exposed populations before such an experiment could be completed.

Clearly, the Chernobyl incident requires a full-scale epidemiologic investigation of the populations exposed. If properly done, an important counterpart to the studies of the Japanese and the radium dial painters and patients might result, thus filling in our knowledge.

(a) Perhaps the attempts to put out the graphite fires by dumping sand, boron compounds, etc., contributed to this (W. J. Bair, January 22, 1987).

(b) Despite the fact that actual data were available only for the early effects, the urgency to make estimates of the biological consequences spawned several evaluations and predictions in 1987. The chapter by Goldman and Catlin in the DOE report (DOE 1987) is quite detailed, but there are abbreviated versions, too (Goldman 1987a,b; Hull 1986, 1987a,b; Marshall 1987; Norman and Dickson 1986; and Gofman 1986). These do not all agree with each other.

Environmental transfer functions must be determined in depth. The knowledge is needed to handle properly the inevitable problems of food and water contamination. It would be very surprising if deviations from the models did not appear in quantity. The next few years provide an opportunity to check out the extant models in the context of the specific event.

Many less important, or less obvious, gaps in our knowledge and needs for further work will undoubtedly appear. However, the biomedical story must unfold first. Meanwhile, the physicists and engineers can busy themselves with the gaps in their knowledge.

F. Where to Find it

To illustrate the general progression of our ideas and of the researches to test them, many specific events were considered in moderate depth in this book. These descriptions, plus the literature cited, may be useful to the reader interested in reviewing, in historical perspective, the development of information pertinent to nuclear energy and nuclear power reactors.

The chapter outlines should be sufficient to guide the reader, but may need to be supplemented by use of the rather extensive subject index. Also, the reader is reminded (see preface) that the scope and mission of this book led to emphasis on U.S. work with, however, frequent references to work in other countries.

1. Physical Events

The phenomena of nuclear fission and the contrast between weapons-produced fission products and reactor fission products are touched upon in chapters 6, 11, and 12. The phenomena of weapons fallout and transport are reviewed briefly in chapter 12, with references for detail. There too are short descriptions of local, tropospheric, and stratospheric modes of transport and the problems of local, nationwide, and global fallout.

Releases of noble gases, of tritium, and of the iodines from reactors and nuclear installations, and transport of the plume are described in chapters 10, 11, and 15. Behavior in the field of released fission products and actinides appear in chapters 12, 14, and 15.

The need for a containment factor as high 10^{-9} is pointed out in connection with the hypothetical Liquid Metal Fast Breeder Reactor, along with a short discussion of our ability to achieve such nearly absolute containment.

2. Phenomena in the Environment

The transport of radionuclides in air, surface, and ground water, and in terrestrial media are considered in chapter 15. Here it becomes obvious that much must be done by modeling. The principal features of environmental modeling are considered in that chapter, with examples involving specific radionuclides.

The contamination of food and water and their possible importance are considered in several places. The basic revelations appear in connection with fallout from weapons tests in chapter 12. Experimental work involving food chains, including soil, is described in chapter 13. This includes individual nuclides and individual organisms. Dietary pathways and dietary usage factors appear prominently in chapter 15. Special environments are considered in both chapter 13 and chapter 15.

Knowledge of the behavior of radionuclides in aquatic environments is diffused through several chapters, primarily chapters 11, 12, and 13. These include the Pacific Ocean and several river systems. Possible effects in environmental systems are spread throughout chapters 11, 12, 13, 14, and 15, but are considered especially in chapter 13.

Environmental experience around nuclear energy sites is concentrated in chapter 11, but some of the polemics generated are reserved for chapter 12, since they involved weapons testing as well as nuclear installations.

3. Generation of Biomedical Information

The early experiments with fission products done during World War II are discussed in chapter 6, while the more sophisticated and long-term experiments with animals are reviewed in chapter 8. These include the now classic experiments with iodine at Hanford, with strontium and plutonium at ANL, Hanford, and the University of Rochester, with cesium at Argonne and Berkeley, with tritium at Hanford and Brookhaven, and effects in the fetal and juvenile mammal, also at Hanford. Inhalation of radioactive gases is reviewed historically in chapter 9 and in more detail in chapter 10.

The monumental long-term experiments with strontium, the actinides, and radium are reviewed in depth in chapter 8 and the story of the radium dial painters in chapter 1.

Comparable long-term experiments, but tied more specifically to the problems of weapons fallout, done at the University of California at Davis (ingestion) and at the Inhalation Toxicology Research Institute, Lovelace Foundation (inhalation), are described briefly^(a) also in chapter 8, but in much more detail in chapters 9 and 13 (Lovelace) and in chapter 13 (Davis). Also, much work leading toward understanding of biological mechanisms is reviewed, especially in chapters 13 and 21.

The reader with limited time and interests primarily in the science as contrasted to phenomenological aspects, might well concentrate on chapters 8 and 13. Conversely, the reader interested primarily in the events, behavior of radioisotopes and their effects may wish to concentrate on chapters 11, 12, and 15, with a light reading of chapter 8.

4. Standards

A full chapter (chapter 16) is devoted to standards for exposure to radiation, with emphasis on radioisotopes and how biomedical research data undergirded the development of standards. Development of population standards is included, and there is some discussion of specific exposure standards for fallout, and emergency exposure levels in general, both there and in chapter 12. The general history of radiation protection standards is given largely by references, since the subject is covered well elsewhere.

The influence of findings regarding the environmental transfer of radionuclides to food and water on the setting and application of standards for nuclear reactors is given special attention in chapter 15.

(a) Several experiments with cesium are included in this work.

G. Is Chernobyl the End of Nuclear Power?(a)

Only time can tell. Reactions have been violent in some parts of the world, and the implications have been made, especially in the United States, that we have an uncontrollable monster in our midst, and it should be destroyed. By contrast, those who really depend on nuclear energy for power are going about business as usual (IAEA 1986). The undamaged reactors at Chernobyl are already back in operation after extensive decontamination. Perhaps no better example is needed of the application of the risk-benefit equation. Somewhere, sometime the best balanced procedures for meeting the power needs of a shrinking world will emerge. Meanwhile, we can only conclude that the biomedical problems of nuclear power (Note: not nuclear war) are probably no more pressing than those, for example, of general chemical contamination, of epidemic diseases, such as AIDS and malaria, and the control of hunger and famine. Only nuclear war can dominate all of these.

NOTE 1

Subject index from Wasserman and Comar (1961): Annotated bibliography of strontium and calcium metabolism in man and animals. This indicates the range of topics under investigation even at that early date.

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*Radioactive.

(a) An evaluation slanted toward the United States has been published by Ahearne (1987).

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References

- Ahearne, J. F. 1987. Nuclear power after Chernobyl. *Science* 236:673-79.
- Arnold, J. S. and W. S. S. Jee. 1957. Bone growth and osteoclastic activity as indicated by radioautographic distribution of plutonium. *Am. J. Anat.* 101:367-418.
- Bair, W. J., ed. 1964. *Inhaled radioactive particles and gases*. Proceedings of the 3d annual Hanford biology symposium held in Richland, Wash., May 4-6, 1964. *Health Phys.* 10(12):861-1259. [Also published in the symposium series of Pergamon Press, New York-Oxford, 1965.]
- Bair, W. J. 1974. Toxicology of plutonium. In *Advances in radiation biology*, eds. J. T. Lett, A. Howard, and M. Zelle, vol.4, pp. 255-315. New York: Academic Press.
- Bair, W. J. 1977. Current status of hot particle issue (A review of relevant experimental and theoretical approaches). In *Recueil des communications—Proceedings*, vol. 3, pp. 703-10. Proceedings of the 4th international congress of the IRPA held in Paris, April 24-30, 1977. Paris: International Radiation Protection Association.
- Bair, W. J., C. R. Richmond, and B. W. Wachholz. 1974. *A radiobiological assessment of the spatial distribution of radiation dose from inhaled plutonium*. WASH-1320. Washington, D.C.: U.S. Atomic Energy Commission.
- Bair, W. J., J. E. Ballou, J. F. Park, and C. L. Sanders. 1973. Plutonium in soft tissues with emphasis on the respiratory tract. Chapter 11 in *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh, pp. 503-68. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.
- Ballou, J. E., ed. 1976. *Radiation and the lymphatic system*, CONF 740930. Proceedings of the 14th annual Hanford biology symposium held in Richland, Wash., September 30-October 2, 1974. Springfield, Va.: National Technical Information Service.
- Ballou, J. E., A. C. Case, and D. L. Haggard. 1984. Disposition of U-232 and daughter radionuclides following intratracheal instillation of $^{232}\text{UO}_2(\text{NO}_3)_2$ in rats. *Health Phys.* 47:210. [Abstract P/56]
- Ballou, J. E., R. L. Buschbom, A. C. Case, G. E. Dagle, R. A. Gies, and J. L. Ryan. 1985. Toxicology of thorium cycle nuclides. In *Pacific Northwest Laboratory annual report for 1984 to the DOE Office of Energy Research, Part 1 Biomedical Sciences*. PNL-5500, pt. 1, pp. 35-37. Richland, Wash.: Pacific Northwest Laboratory.
- Barendsen, G. W. 1964. Impairment of the proliferative capacity of human cells in culture by α -particles with differing linear-energy transfer. *Int. J. Radiat. Biol. & Relat. Stud. Phys. Chem. & Med.* 8:453-66.

- Barendsen, G. W. 1967. Mechanism of action of different ionizing radiations on the proliferative capacity of mammalian cells. *Theor. Exp. Biophys.* 1:167.
- Bauer, G. C. H., A. Carlsson, and B. Lindquist. 1961. Metabolic and homeostatic function of bone. In *Mineral metabolism*, vol. 1, pt. B, pp. 609-76. New York: Academic Press.
- Benjamin, S. A., R. K. Jones, M. B. Snipes, and C. S. Lustgarten. 1976. Comparative effects of inhaled relatively insoluble forms of ^{90}Y , ^{144}Ce , and ^{90}Sr on canine peripheral lymphocyte function. In Ballou 1976, pp. 90-99.
- Boyd, J., W. F. Neuman, and H. C. Hodge. 1958. *On the mechanisms of skeletal fixation of strontium*. UR-512. Rochester, N.Y.: Univ. of Rochester.
- Brooks, A. L., R. J. LaBauve, R. O. McClellan, and D. A. Jensen. 1976. Chromosome aberration frequency in blood lymphocytes of animals with ^{239}Pu lung burdens. In Ballou 1976, pp. 106-12.
- Bruenger, F. W., J. M. Smith, D. R. Atherton, W. S. S. Jee, R. D. Lloyd, and W. Stevens. 1983. Skeletal retention and distribution of ^{226}Ra and ^{239}Pu in beagles injected at ages ranging from 2 days to 5 years. *Health Phys.* 44, Suppl. 1:513-27.
- Casarett, G. W. 1973. Pathogenesis of radionuclide-induced tumors. In *Radionuclide carcinogenesis*, eds. C. L. Sanders, R. H. Busch, J. E. Ballou, and D. D. Mahlum, CONF-720505, pp. 1-14. Proceedings of the 12th annual Hanford biology symposium held in Richland, Wash., May 10-12, 1972. Springfield, Va.: National Technical Information Service.
- Casarett, L. J. 1960. Some physical and physiological factors controlling the fate of inhaled substances—II. Retention. *Health Phys.* 2:379-86.
- Clarke W. J. 1962. Comparative histopathology of Pu^{239} , Ra^{226} , and Sr^{90} in pig bone. *Health Phys.* 8:621-27.
- Cothern, C. R. and J. E. Smith, eds. 1987. *Environmental radon*. New York: Plenum Press.
- Cross, F. T. and W. J. Bair. 1984. Mean dose versus local dose to the respiratory tract—Implications for radiological protection. In *Lung modelling for inhalation of radioactive materials*, EUR-9384, pp. 303-19. Proceedings of a symposium held in Oxford, March 26-28, 1984. Brussels: Commission of the European Communities.
- Department of Energy. 1987. Health and environmental consequences of the Chernobyl nuclear power plant accident. DOE/ER-0332. Springfield, Va.: National Technical Information Service.
- Department of Health and Human Services. 1984. *Oncology overview—Selected abstracts on risk of cancer from exposure to low-level ionizing radiation*, V. E. Archer [consulting reviewer], PB 84-922906, NCI/CRDB/OK84/06. Washington, D.C.: U.S. DHHS, National Cancer Institute, International Cancer Research Data Bank Program.
- DHHS. See Department of Health and Human Services.
- Dobson, E. J., J. W. Gofman, H. B. Jones, L. S. Kelly, and L. J. Walker. 1948. *Studies with colloids containing radioisotopes of yttrium, zirconium, columbium, and lanthanum. II. The controlled selective localization of radioisotopes of yttrium, zirconium and columbium in the bone marrow, liver, and spleen*. AEC-D-2055. Manuscript date April 21, 1948, declassified June 16, 1948. Washington, D.C.: U.S. Atomic Energy Commission.
- DOE. See Department of Energy.
- Durbin, P. W. 1984 and 1986a. Metabolic models for uranium. In *Biokinetics and analysis of uranium in man*, ed. R. H. Moore, USUR-05, HEHF-47, pp. F-1-F-65. Proceedings of a workshop sponsored by the U.S. Uranium Registry held in Richland, Wash., August 8-9, 1984. Richland, Wash.: Hanford Environmental Health Foundation.
- Durbin, P. W. 1986b. Personal discussion, October 17, 1986. [Specifically in connection with neptunium, but had generic extensions.]
- Durbin, P. W., M. W. Horovitz, and E. R. Close. 1972. Plutonium deposition kinetics in the rat. *Health Phys.* 22:731-41.
- Dymling, J. F. 1962. Accretion and excretory clearance rates and exchangeable spaces measured in man with Ca^{47} and Sr^{85} under normal and pathological conditions. In *Medical uses of Ca^{47}* , technical report series no. 10, pp. 73-76. Vienna: International Atomic Energy Agency.

- Eidson, A. F. 1981. *Biological characterization of radiation exposure and dose estimates from inhaled uranium milling effluents*. NUREG/CR-2539, LMF-94, RH. Washington, D.C.: U.S. Nuclear Regulatory Commission.
- Eisenbud, M. 1986. The reactor accident at Chernobyl nuclear power station in the USSR, April 26, 1986. Addition to 3d ed. of *Environmental radioactivity*, pp. 375-88. New York: Academic Press.
- Energy Research and Development Administration. 1975. Excerpt from planning document concerning inhalation problems associated with energy production. Washington, D.C.: U.S. ERDA, Division of Biological and Environmental Research.
- Engström, A., R. Björnerstedt, C.-J. Clemedson, and A. Nelson. 1957. *Bone and radiostrontium*. New York: John Wiley & Sons.
- ERDA. See U.S. Energy Research and Development Administration.
- Evans, R. D. 1983. Highlights of the meeting—Invited summary. In *Proceedings of an international conference on radiobiology of radium and the actinides in man*. [Also in *Health Phys.* 44, Suppl. 1:571-73.]
- Finkel, M. P. and B. O. Biskis. 1969. Osteosarcomas induced in mice by FBJ virus and ^{90}Sr . In *Delayed effects of bone-seeking radionuclides*, eds. C. W. Mays, W. S. S. Jee, R. D. Lloyd, B. J. Stover, J. H. Dougherty, and G. N. Taylor, pp. 417-435. Salt Lake City: Univ. of Utah Press.
- Finkel, M. P., B. O. Biskis, and P. B. Jinkins. 1966. Virus induction of osteosarcomas in mice. *Science* 151:698-701.
- Finkel, M. P. and C. A. Reilly, Jr. 1973. Observations suggesting the viral etiology of radiation-induced tumors, particularly osteogenic sarcomas. In *Radionuclide carcinogenesis*, eds. C. L. Sanders, R. H. Busch, J. E. Ballou, and D. D. Mahlum, CONF-720505, pp. 278-88. Proceedings of the 12th annual Hanford biology symposium held in Richland, Wash., May 10-12, 1972. Springfield, Va.: National Technical Information Service.
- Frazier, M. E., J. E. Lund, and R. H. Busch. 1976. In vitro injections of lymphocytes and cultured cells from beagles with plutonium-induced bone tumors. In Ballou 1976, pp. 197-202.
- Frazier, M. E., R. N. Ushijima, and E. B. Howard. 1970. Virus association with ^{90}Sr induced leukemia of miniature swine. In *Bibliotheca haematologica*, no. 36: *Comparative leukemia research*, ed. R. M. Dutcher, pp. 440-45. Basel: Karger.
- Fukuda, S. and J. D. Kopple. 1980. Chronic uremia syndrome in dogs induced with uranyl nitrate. *Nephron*. 25:139-43.
- Gofman, J. W. 1949. Studies with colloids containing radioisotopes of yttrium, zirconium, columbium, and lanthanum. I. The chemical principles and methods involved in preparation of colloids of yttrium, zirconium, columbium, and lanthanum. *J. Lab. Clin. Med.* 34:297-304. II. The controlled selective localization of radioisotopes of yttrium, zirconium, and columbium in the bone marrow, liver, and spleen, eds. E. L. Dobson, J. W. Gofman, H. B. Jones, L. S. Kelly, and L. A. Walker. *J. Lab. Clin. Med.* 34:305-12.
- Gofman, J. W. 1986. Report of program on Station WAMU-FM, Washington, D.C., December 12, 1986. The Fred Fisher Show. From memo addressed to Department of Energy by Radio-TV Reports, Inc., Chevy Chase, Md.
- Goldman, M. 1981. The radiotoxicity of uranium. Chapter prepared for a committee of the National Academy of Sciences. [Sent to the author as a personal communication from Dr. Goldman.]
- Goldman, M. 1987a. Chernobyl: A radiobiological perspective. *Science* 238:622-23.
- Goldman, M. 1987b. Chernobyl radiation dose. *Science* 237:575 [letter by Goldman].
- Gross, P. 1964. The processes involved in the biologic aspects of pulmonary deposition, clearance, and retention of insoluble aerosols. *Health Phys.* 10:995-1002.
- Hahn, O. 1936. *Applied radiochemistry*. Ithaca, N.Y.: Cornell Univ. Press.
- Häissinsky, M. 1934. *Les radiocolloïds*. Actualités scientifiques et industrielles. Paris: Hermann et Cie.
- Heogerman, S. F., H. T. Cummins, and J. F. Bronec. 1976. Chromosome breakage in lymphocytes from humans with body burdens of ^{226}Ra . In Ballou 1976, pp. 113-19.
- Hines, N. O. 1976. *Fish of rare breeding, salmon and trout of the Donaldson strains*. Washington, D.C.: Smithsonian Institution Press.

- Hull, A. P. 1986. Preliminary dose assessment of the Chernobyl accident. Part I. *Health Physics Society Newsletter*, vol. 14, no. 12, December 1986.
- Hull, A. P. 1987a. Preliminary dose assessment of the Chernobyl accident. Part II. *Health Physics Society Newsletter*, vol. 15, no. 1, January 1987.
- Hull, A. P. 1987b. Preliminary dose assessment of the Chernobyl accident. Part III. *Health Physics Society Newsletter*, vol. 15, no. 2, February 1987.
- IAEA. See International Atomic Energy Agency.
- ICRP. See International Commission on Radiological Protection and Measurements.
- International Atomic Energy Agency. 1986. *The accident at the Chernobyl Nuclear Power Plant and its consequences*. A report prepared by the USSR State Committee on the Utilization of Atomic Energy presented to a meeting of experts sponsored by the International Atomic Energy Agency in Vienna, August 25-29, 1986.
- International Commission on Radiological Protection and Measurements. 1972. Alkaline earth metabolism in adult man. ICRP pub. 20. *Annals of the ICRP*. Also *Health Phys.* 24:125-221.
- International Commission on Radiological Protection and Measurements. 1979. Limits for intakes of radionuclides by workers. ICRP Pub. 30, pt. 1. *Annals of the ICRP*, vol. 2, nos. 3/4. New York-Oxford: Pergamon Press.
- International Commission on Radiological Protection and Measurements. 1980. Biological Effects of Inhaled Radionuclides. ICRP pub. 31. *Annals of the ICRP*, vol. 4, nos. 1/2. New York-Oxford: Pergamon Press.
- Jee, W. S. S. and J. S. Arnold. 1961. The toxicity of plutonium deposited in skeletal tissues of beagles. I. The relation of the distribution of plutonium to the sequence of histopathologic bone changes. *Lab. Invest.* 10:797-825.
- Jee, W. S. S. and J. S. Arnold. 1962. The failure of plutonium to deposit in the osteoid of rachitic rats. *Health Phys.* 8:709-11.
- Jones, D. C. and D. H. Copp. 1948. *Studies of bone metabolism with the aid of radioactive strontium*. AECD-1962, issued January 16, 1948, declassified April 22, 1948. Washington, D.C.: U.S. Atomic Energy Commission.
- Jones, H. B., C. J. Wrobel, and W. R. Lyons. 1944. A method for distributing beta-radiation to the reticulo-endothelial system and adjacent tissues. *J. Clin. Invest.* 23:783-88.
- Jones, R. K., B. B. Boecker, J. A. Pickrell, C. H. Hobbs, and R. O. McClellan. 1976. Influence of radiation-dose pattern from inhaled beta-gamma-emitting radionuclides on canine peripheral lymphocytes. In Ballou 1976, pp. 83-89.
- Larsen, R. P., R. D. Oldham, and R. E. Toohey. 1981. Macrodistribution of plutonium in the human skeleton. In *Actinides in man and animals*, ed. M. E. Wrenn, pp. 191-97. Proceedings of the Snowbird actinide workshop held in Snowbird, Utah, October 15-17, 1979. Salt Lake City: RD Press.
- Lyaginskaya, A. M., Yu. I. Moskalev, I. V. Filyushkin, M. D. Ponerantseva, L. K. Ramaiya, S. I. Dementyev, and V. A. Schevchenko. 1985. *Biological grounds for clarification of safety standards for internal exposure of the gonads*. [Paper made available at meeting of Committee 2 of ICRP, Washington, D.C. and transmitted by W. J. Bair, Richland, Wash.]
- Macklis, R. M., B. M. Kinsey, A. I. Kassis, J. L. M. Ferrara, R. W. Atcher, J. J. Hines, C. N. Coleman, S. J. Adelstein, and S. J. Burakoff. 1988. Radioimmunotherapy with alpha-particle-emitting immunoconjugates. *Science* 240:1024-26.
- Marshall, E. 1987. Recalculating the cost of Chernobyl. *Science* 236:658-59. [A review of Goldman's views and the chapter from DOE 1987.]
- Marshall, J. H. 1960a. *Radioactive hotspots, bone growth, and bone cancer*. ANL-6297, pp. 16-26. Argonne, Ill.: Argonne National Laboratory.
- Marshall, J. H. 1960b. *Some calculations of the non-uniformity factor in the induction of bone cancer by internal emitters*. ANL-6199, pp. 55-61. Argonne, Ill.: Argonne National Laboratory.
- Marshall, J. H. 1962. Radioactive hotspots, bone growth, and bone cancer: Self-burial of calcium-like hotspots. In *Radioisotopes and bone*, eds. Lacroix and Budy, pp. 35-50. Philadelphia, Pa.: F. A. Davis Co.

- Marshall, J. H. 1963. *Theory of alkaline earth metabolism*. ANL-6646, pp. 5-29. Argonne, Ill.: Argonne National Laboratory.
- Marshall, J. H. 1968. *A model for the remodeling and exchange rate distributions in adult human bone*. ANL-7615, pp. 58-76. Argonne, Ill.: Argonne National Laboratory.
- Marshall, J. H. 1970. *A comprehensive model of alkaline earth metabolism*. ANL-7760, pt. 2, pp. 95-109. Argonne, Ill.: Argonne National Laboratory.
- Marshall, J. H. and M. P. Finkel. 1959. *Autoradiographic dosimetry of mouse bones containing Ca^{45} , Sr^{90} , and Ra^{226}* . ANL-6104, pp. 48-65. Argonne, Ill.: Argonne National Laboratory.
- Marshall, J. H. and M. P. Finkel. 1960. *Autoradiographic dosimetry of mouse bones containing Ca^{45} , Sr^{90} or Ra^{226} . II. The sensitive region in the induction of osteogenic sarcomas*. ANL-6199, pp. 44-54. Argonne, Ill.: Argonne National Laboratory.
- Marshall, J. H. and R. E. Rowland. 1958. *Microscopic metabolism of calcium in bone*. ANL-5967, pp. 67-79. Argonne, Ill.: Argonne National Laboratory.
- Marshall, J. H., R. E. Rowland, and J. Jowsey. 1956. *Quantitative autoradiographic measurement of calcium-45 concentrations in cortical bone*. ANL-5679, pp. 48-62. Argonne, Ill.: Argonne National Laboratory.
- Marshall, J. H., V. K. White, and J. Cohen. 1957. *Three-dimensional deposition of calcium-45 in cortical bone of dogs*. ANL-5755, pp. 5-17. Argonne, Ill.: Argonne National Laboratory.
- McLean, F. C. and A. M. Budy. 1964. *Radiation, isotopes, and bone*. New York: Academic Press.
- Meneely, G. R., ed. 1961. *Radioactivity in man*. Springfield, Ill.: Charles C. Thomas.
- Mercer, T. T. 1973. *Aerosol technology in hazard evaluation*. New York: Academic Press.
- Morrow, P. E. 1960. Some physical and physiological factors controlling the fate of inhaled substances—I. Deposition. *Health Phys.* 2:366-78.
- Morrow, P. E. 1964. Evaluation of inhalation hazards based upon the respirable dust concept and the philosophy and application of selective sampling. *J. Am. Ind. Hyg.* 25:213-36.
- Morrow, P. E., et al. 1982. *Metabolic fate and evaluation of injury in rats and dogs following exposure to the hydrolysis products of uranium hexafluoride*. NUREG/CR-2268. Washington, D.C.: U.S. Nuclear Regulatory Commission.
- NAS-NRC. See National Academy of Sciences-National Research Council.
- National Academy of Sciences-National Research Council. 1961. *Effects of inhaled radioactive particles*. NAS-NRC publ. 848. Washington, D.C.
- National Council on Radiation Protection and Measurements. 1975. *Alpha-emitting particles in lungs*. NCRP report no. 46. Bethesda, Md.
- National Council on Radiation Protection and Measurements. 1987. *Genetic effects from internally deposited radionuclides*. NCRP report no. 89. Bethesda, Md.
- NCRP. See National Council on Radiation Protection and Measurements.
- Neuman, W. F. and M. W. Neuman. 1958. *The chemical dynamics of bone mineral*. Chicago, Ill.: Univ. of Chicago Press.
- Norman, C. and D. Dickson. 1986. The aftermath of Chernobyl. *Science* 233:1141-43.
- Paneth, F. 1928. *Radioelements as indicators*, chapter 6. New York: McGraw-Hill.
- Park, J. F., W. J. Bair, and R. H. Busch. 1972. Progress in beagle dog studies with transuranium elements at Battelle-Northwest. *Health Phys.* 22:803-10. [Also progress reports with approximately the same title in the annual reports over many years.]
- Ragan, H. A., J. F. Park, R. J. Olson, and R. L. Buschbom. 1976. Lymphocytopenia induced in beagle dogs by inhalation of $^{239}\text{PuO}_2$. In Ballou 1976, pp. 100-105.
- Reilly, C. A., Jr. and M. P. Finkel. 1971. Evidence of FBJ virus antigen in ^{90}Sr -induced osteosarcomas. *Radiat. Res.* 47:252-53.
- Roesch, W. C. 1977. Microdosimetry of internal sources. *Radiat. Res.* 70:494-510.
- Rossi, H. H. 1967. Energy distribution in the absorption of radiation. In *Advanced Biological and Medical Physics*, eds. J. H. Lawrence and J. W. Gofman, vol. 11, pp. 27-85. New York: Academic Press.
- Rothstein, A. 1983. Letter to J. N. Stannard dated December 20, 1983.

- Rowland, R. E. 1960. *Microscopic metabolism of Ra²²⁶ in canine bone*. ANL-6199, pp. 16-20. Argonne, Ill.: Argonne National Laboratory.
- Rowland, R. E. 1961. *Skeletal retention of the alkaline earth radioisotopes and bone dosimetry*. ANL-6398, p. 40. Argonne, Ill.: Argonne National Laboratory.
- Rowland, R. E. and J. H. Marshall. 1958. *Microscopic metabolism of Ra²²⁶ in canine bone*. ANL-5967, pp. 58-66. Argonne, Ill.: Argonne National Laboratory.
- Sanders, C. L. 1969. The biological behavior of ²³⁹PuO₂ particles: Role of the peritoneal mononuclear phagocyte. *Radiat. Res.* 38:125-34.
- Sanders, C. L. 1970. Maintenance of phagocytic function following ²³⁹PuO₂ particle administration. *Health Phys.* 18:82-85.
- Sanders, C. L. 1972. Deposition patterns and the toxicity of transuranium elements in lung. *Health Phys.* 22:607-15.
- Sanders, C. L. and R. R. Adey. 1970. Ultrastructural localization of inhaled ²³⁹PuO₂ particles in alveolar epithelium and macrophages. *Health Phys.* 18:293-95.
- Sanders, C. L. and J. F. Park. 1971. Pulmonary distribution of alpha dose from ²³⁹PuO₂ and induction of neoplasia in rats and dogs. In *Inhaled particles. III*, ed. W. H. Watson, vol. 1, pp. 489-98. Proceedings of a symposium held in London, September 14-23, 1970. Old Woking, Surrey, England: Unwin Bros., Ltd.
- Sanders, C. L., F. T. Cross, G. E. Dagle, and J. A. Mahaffey, eds. 1980. *Pulmonary toxicology of respirable particles*, CONF-791002. Proceedings of the 19th annual Hanford life sciences symposium held in Richland, Wash., October 22-24, 1979. Springfield, Va.: National Technical Information Service.
- Sanders, C. L., R. D. Schneider, G. E. Dagle, and H. A. Ragan, eds. 1977. *Pulmonary macrophage and epithelial cells*, CONF-760927. Proceedings of the 16th annual Hanford biology symposium held in Richland, Wash., September 27-29, 1976. Springfield, Va.: National Technical Information Service.
- Schlenker, R. A. and B. G. Oltman. 1981. Plutonium microdistribution in human bone. In *Actinides in man and animals*, ed. M. E. Wrenn, pp. 199-206. Proceedings of the Snowbird actinide workshop held in Snowbird, Utah, October 15-17, 1979. Salt Lake City: RD Press.
- Schlenker, R. A., B. G. Oltman, and H. T. Cummins. 1976. Microscopic distribution of ²³⁹Pu deposited in bone from a human injection case. In *The health effects of plutonium and radium*, ed. W. S. S. Jee, pp. 321-328. Salt Lake City: The J. W. Press.
- Schubert, J. 1948. *The radiocolloidal properties of some fission products*. AECD-1910. Manuscript date February 11, 1948, declassified April 20, 1948. Washington, D.C.: U.S. Atomic Energy Commission.
- Schweitzer, G. K. and W. M. Jackson. 1952. Studies in low concentration chemistry. I. The radiocolloidal properties of lanthanum-140. *J. Am. Chem. Soc.* 74:4178-80.
- Schweitzer, G. K., B. R. Stein, and W. M. Jackson. 1953. Studies in low concentration chemistry. III. The radiocolloidal properties of yttrium-90. *J. Am. Chem. Soc.* 75:793-95.
- Spiers, F. W. 1968. *Radioisotopes in the human body: Physical and biological aspects*. New York: Academic Press.
- Stannard, J. N. 1959. An evaluation of inhalation hazards in the nuclear energy industry. In *Progress in nuclear energy*, eds. W. G. Marley and K. Z. Morgan, vol. 1, pp. 40-51 [also vol. 2, pp. 70-82]. New York: Pergamon Press.
- Stannard, J. N. 1976. Summary and comments. In Ballou 1976, pp. 246-48.
- Stannard, J. N. 1984 and 1986. Uranium and man. In *Biokinetics and analysis of uranium in man*, ed. R. H. Moore. USUR-05, HEHF-47, pp. C-1-C-26. Proceedings of a workshop sponsored by the U.S. Uranium Registry held in Richland, Wash., August 8-9, 1984 [keynote address]. Richland, Wash.: Hanford Environmental Health Foundation.
- Stannard, J. N. and G. W. Casarett. 1964. Concluding comments on biological effects of alpha-particle emitters in soft tissue as exemplified by experiments with polonium 210. *Radiat. Res. Suppl.* 5:398-434.
- Stover, B. J. 1972. Life shortening consequent to internal irradiation from ²³⁹Pu. *Health Phys.* 22:823-27.

- Task Group on Lung Model. 1966. Deposition and retention models for internal dosimetry of the human respiratory tract. *Health Phys.* 12:173-207.
- Taylor, D. M. 1973. Chemical and physical properties of plutonium. Chapter 9 in *Uranium, plutonium, transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, J. B. Hursh, pp. 323-47. Handbook of experimental pharmacology, new series, vol. 36. New York: Springer-Verlag.
- TGLM. See Task Group on Lung Model, also known as TGLD, Task Group on Lung Dynamics.
- Thomas, R. G. 1964. Influence of aerosol properties upon gross distribution and excretion. *Health Phys.* 10:1013-28.
- Thomas, R. G. 1984. Letter to J. N. Stannard dated November 26, 1984.
- Thompson, R. C. 1952. Studies of metabolic turnover with tritium as a tracer. I. Gross studies on the mouse. *J. Biol. Chem.* 197:81-87.
- Thompson, R. C. 1953. Studies of metabolic turnover with tritium as a tracer. II. Gross studies on the rat. *J. Biol. Chem.* 200:731-43.
- Thompson, R. C. 1967. Biological factors. Chapter 23 in *Plutonium handbook: A guide to the technology*, ed. O. J. Wick, vol. 2, pp. 785-829. New York: Gordon & Breach.
- Thompson, R. C. In press. A legacy of life-span dog studies. In Radiation protection—A look to the future. Proceedings of the 25th annual Hanford life sciences symposium held in Richland, Wash., October 21-23, 1986 [poster session]. *Health Phys.*: in press.
- Thompson, R. C. and J. E. Ballou. 1954. Studies of metabolic turnover with tritium as a tracer. IV. Metabolically inert lipid and protein fractions from the rat. *J. Biol. Chem.* 208:883-88.
- Thompson, R. C. and J. E. Ballou. 1956. Studies of metabolic turnover with tritium as a tracer. V. The predominantly non-dynamic state of body constituents in the rat. *J. Biol. Chem.* 223:795-809.
- Thompson, R. C. and J. A. Mahaffey, eds. 1986. *Life-span radiation effects studies in animals: What can they tell us?* CONF-830951 (DE 87000490). Proceedings of the 22d annual Hanford life sciences symposium held in Richland, Wash., September 27-29, 1983. Springfield, Va.: National Technical Information Service.
- Upton, A. C. 1976. Reflections of a wayfarer in radiation research. In Ballou 1976, pp. 73-76.
- U.S. Congress. 1961. *Applications of radioisotopes and radiation in the life sciences*. Hearings before the Joint Committee on Atomic Energy, 87th Cong., 1st sess. Special Subcommittee on Research, Development, and Radiation, March 27, 28, 29, and 30, 1961. Washington, D.C.: U.S. Government Printing Office.
- Vaughan, J. in collaboration with B. Bleaney and D. Taylor. 1973. Distribution, excretion and effects of plutonium as a bone-seeker. Chapter 10 in *Uranium, plutonium, the transplutonic elements*, eds. H. C. Hodge, J. N. Stannard, and J. B. Hursh, pp. 349-502. Handbook of Experimental Pharmacology, new series, vol. 36. New York: Springer-Verlag.
- Wasserman, R. H. and C. L. Comar. 1961. *Annotated bibliography of strontium and calcium metabolism in man and animals*. U.S. Department of Agriculture publ. no. 821. Washington, D.C.: U.S. Government Printing Office.
- WHO. See World Health Organization.
- Wilson, R. 1987. A visit to Chernobyl. *Science* 236:1636-40.
- World Health Organization. 1986a. Updated background information on the nuclear reactor accident in Chernobyl, USSR, June 12, 1986.
- World Health Organization. 1986b. Working group on assessment of radiation dose commitment in Europe due to the Chernobyl accident. July 22, 1986.
- Wrenn, M. E., P. W. Durbin, B. Howard, J. Lipsztein, J. Rundo, E. T. Still, and D. L. Willis. 1985. Metabolism of ingested uranium and radium. *Health Phys.* 48:601-33.

Appendix A

The Interviews

A very important feature in the preparation of this book was the opportunity to meet personally with over one hundred of the investigators who played a part in the history described. Some are "patriarchs" whose work forms the basis for entire areas of the research described, who have (or had) been active for fifty years or more, and who did much to shape the entire field we are calling radioisotope toxicology. Others are key figures of the second generation who shaped the major programs of the "Golden Era" described in chapter 8. Still others are specialists in certain aspects whose contributions made possible the exploration of avenues that might otherwise have remained undeveloped. A few are relatively recent arrivals, who have a grasp nonetheless of the history behind them and who have assumed responsibility for the future.

Unfortunately, a few of those interviewed in the early phases of preparation are no longer with us. Perhaps we need no more forceful indication that it was high time this history was written.

Despite the effort expended on interviews, this book cannot and should not be termed an oral history. The results of the conversations were always used to confirm and extend, or to add anecdotal flavor to the unfolding written stories of the research programs. The reports and published literature formed the basic structure that the interview results then fleshed out and made more personal, frequently more specific, even more correct. Thus, the book is a combination of oral history and conventional digging into the literature. Both were enjoyable and revealing, but the personal interviews were especially stimulating and pleasant.

Unfortunately, as the project grew in size, it was necessary to eschew information gained in the interviews, as it was necessary to discard parts of the written record. It is hoped that some other opportunity will be presented to air these items, particularly anecdotal material.

The author is most grateful to the many friends and colleagues who extended time and talent, sometimes more than once, and sometimes for many hours at a stretch, to recall details of what was done, how it was done, and the milieu existing at the time it was done. Some of the interviews lasted less than an hour; a few required the better part of two days. Obviously, they concentrated on each individual's personal research interests, but sometimes much broader topics occupied the stage. Sometimes those interviewed had been asked to read,

prior to the interview, a draft copy of a chapter pertinent to their experience. The discussion was then built upon a critique of something already written. Most often, however, the interview was an occasion for sheer recall and commentary.

A majority of the interviews were taped and later transcribed. Both are being readied for deposit in a suitable repository after they have been edited. Unfortunately, in the early efforts, the author used tapes that did not hold up well, and the record of those interviews must be limited to notes.

In the listing that follows, the interviews are arranged alphabetically by last name. Also, the individual's base of operations and the position or field of operation at the time of the interview or prior to retirement are given. For the reader's convenience, there is also an indication of the principal subject matter discussed. Most of the discussions took place at the interviewee's home base, and sometimes they became a group affair as colleagues joined in. Other interviews took place at national scientific meetings, from which the individual was willing to break away for an hour or so. Still others were at the site of the individual's place of retirement.

There is no doubt that these person-to-person encounters contributed importantly to the text. Sometimes their contribution is obvious and direct and can be referenced formally. In other cases, indeed the majority, the interview contributed primarily to the general flavor of what was going on, or it confirmed or modified the written record. These could seldom be cited directly. Hence, the need for this Appendix.

Financial support for travel and other expenses came from the U.S. Department of Energy through Pacific Northwest Laboratory and is acknowledged with gratitude.

Note: Principal subject matter follows each entry.

Name and Position	Institution	Date(s)
Agnew, Harold , President formerly Director of Los Alamos Scientific Laboratory Work at Met Lab and at research.	GA Technology, La Jolla, CA (formerly General Atomics) Los Alamos Los Alamos during World War II, also early postwar	May 2, 1980
Alpen, Edward Director of Donner Laboratory Naval Radiological Defense Laboratory.	University of California at Berkeley	May 15, 1978, plus discussion in April 1984
Anders, Roger Archivist History of AEC.	AEC, ERDA, DOE Headquarters Germantown.	March 16, 1979
Andrews, Howard L. Professor of Radiation Biology & Biophysics USPHS (retired in Jamestown, R.I.) Instrumentation, weapons tests, general.	University of Rochester National Institutes of Health	September 1980, and many letters since

Name and Position	Institution	Date(s)
Auerbach, Stanley Director, Radioecology Div. Growth and development of radioecology program at Oak Ridge.	Oak Ridge National Laboratory	April 19, 1979
Auxier, John , Head, Health and Safety Research. Oak Ridge programs	Oak Ridge National Laboratory Applied Science Laboratories, Oak Ridge	April 13, 1979
Bair, William J. , Manager, Biomedical and Environmental Research Program. Contract officer for this book. Manager, Life Sciences Center All aspects, particular emphasis on inhalation toxicology:	Battelle, Pacific Northwest Laboratories	June 12, 1979, plus numerous consultations
Bale, William F. , Professor of Radiation Biology and Biophysics. (deceased) Nuclear medicine, radioactive antibodies, research at Rochester during World War II, his work at Georgia Tech since "retirement."	University of Rochester Medical Center Georgia Tech	November 5-6, 1979
Ballou, John Staff Scientist Research at Hanford and Battelle-Northwest.	Battelle, Pacific Northwest Laboratories	June 5, 1979
Baum, John Safety and Environmental Protection Division Marshallese dosimetry.	Brookhaven National Laboratory	September 17, 1982
Bennett, Robert Professor of Radiology History of nuclear medicine and his research.	University of California Los Angeles, Medical Center	February 8, 1979, also 1981, and letters
Bernard, Robert Staff Scientist Uranium research, metabolic models.	Oak Ridge National Laboratory	April 17, 1979
Bethard, William F. Staff Physician His role at Chicago during the 1940s. Biomedical work at GA.	GA Technology, La Jolla, CA (formerly General Atomics)	July 17, 1978
Boecker, Bruce Assistant Director Thorium, field tests, bioassay, metabolic models.	Inhalation Toxicology Research Institute, Albuquerque	September 26, 1981
Bond, Victor Director, Medical Division Medical dosimetry, his experiences with the Marshallese, cellular aspects of nuclear medicine, cellular models.	Brookhaven National Laboratory	September 16, 1982
Bonham, Kelshaw Professor in College of Fisheries (retired) The University of Washington Fisheries program. Joint interview with Larson and Welander.	University of Washington	June 1, 1979

Name and Position	Institution	Date(s)
Brucer, Marshall Medical Director (retired in Tucson, Arizona) The Oak Ridge medical program, history of nuclear medicine, fallout.	Oak Ridge Institute of Nuclear Studies	December 5, 1979
Brues, Austin Scientific Staff, Institute for Human Radiobiology. Former Director, Biology Division Radium cases, program at Argonne, radium pharmacokinetics.	Argonne National Laboratory	September 8, 1978, October 8, 1981, and several follow-up discussions and letters
Bruner, David, Staff, Division of Biology and Medi- cine, and subsequent entities Entire program. Special emphasis on inhalation problems. Interviewed in Florida where he is now retired.	AEC, ERDA, DOE	November 14, 15, 1979
Burr, William, Director Division of Biological and Environmental Research His view of the internal emitter program in all three agencies, especially AEC history.	AEC, ERDA, DOE Headquarters Germantown Now at Oak Ridge Associated Universities and CARL	March 13, 1979, and subsequent follow-ups
Bustad, Leo, Dean, College of Veterinary Medicine formerly Director of AEC program formerly Staff Scientist General history of the Hanford programs, particularly large animal work plus corollaries from his other experiences, sheep exposures at NTS.	Washington State University University of California, Davis Hanford Biology Operations	September 25, 1981, and follow-up letters
Carsten, Arland Medical Department Tritium, nuclear medicine.	Brookhaven National Laboratory	July 1982, September 1982
Carter, Melvin, Professor, Nuclear Engineering The PHS program at Southwestern Radiological Health Laboratory, at NTS, and current work at Georgia Tech.	Georgia Institute of Technology Formerly U.S. Public Health Service, several laboratories	April 10, 1979, and several subsequent letters
Carter, Nicholas Division of Biological and Environmental Research General	DOE Headquarters, Germantown	March 13, 1979
Casarett, George Professor of Radiation Biology and Biophysics and of Radiology Pathology work in MED days, polonium experiments at Rochester, general.	University of Rochester Medical Center	May 28, 1978, May 15, 1979

Name and Position	Institution	Date(s)
Claus, Walter Special Assistant, Division of Biology and Medicine All aspects of program, especially the large animal experiments. Interviewed in Florida where he is now retired.	AEC and ERDA Headquarters Germantown	November 16, 1979, and several sub- sequent visits
Cloutier, Roger Scientist, Medical Division Dosimetry, MIRD, nuclear medicine, epidemiology.	Oak Ridge Institute of Nuclear Studies	July 12, 1979
Cohn, Stanton Medical Department NRDL, Marshallese, current work at Brookhaven in whole-body counting and problems of bone.	Brookhaven National Laboratory	September 16, 1982
Collins, Donald President Instrumentation experience in MED and weapons tests.	Don L. Collins and Associates, Glendale, CA	October 13, 1978
Cowan, Frederick Director, Health Physics (retired) WASH 740, BNL research, both health physics and environmental. Interviewed at scientific meeting and at his home in Florida.	Brookhaven National Laboratory	July 10, 1979, April 1984
Cronkite, Eugene Medical Department Marshallese, NRDL, nuclear medicine.	Brookhaven National Laboratory	September 15, 1982
Cross, Fredrick Scientist Radon and uranium miners, animal work with radon. Joint interview with Ray Palmer.	Battelle, Pacific Northwest Laboratories	June 4, 1979, and sev- eral subsequent con- versations and letters
Deal, Joe Fallout problems.	DOE Headquarters Germantown	March 16, 1979, March 31, 1980
Donaldson, Lauren Professor, School of Fisheries Fisheries program at University of Washington, Pacific studies, marine ecology.	University of Washington	May 31, 1979, October 7, 1983
Dounce, Alexander Professor of Biochemistry (emeritus) Uranium work during MED days.	University of Rochester Medical Center	June 19, 1978
Drew, Robert Inhalation Facility Inhalation toxicology.	Brookhaven National Laboratory	September 15, 1982
Durbin, Patricia , Scientist, Lawrence Radiation Laboratory MED work at Berkeley with J. Hamilton, laboratory research on actinides, bone, uranium, standards. First interview in San Diego, second at Berkeley.	University of California, Berkeley	October 31, 1979, October 1980, and subsequent letters

Name and Position	Institution	Date(s)
Eisenbud, Merrill Professor, Institute of Environmental Medicine Work of HASL, fallout, Sterling Forest, Brazil, work at NYU.	New York University Now at Chapel Hill, NC	July 9, 1979, and subsequent discussions
Evans, Robley Professor of Physics (retired) Radium story, radon and uranium miners' standards. Also the Institute for Human Radiobiology at Argonne. Interviews at Scottsdale, Arizona, where Dr. Evans has retired.	Massachusetts Institute of Technology	April 16, 26, 1978, and several subse- quent letters
Facer, Gordon Formerly classified literature.	U.S. Department of Energy	April 7, 1980
Fairchild, Ralph, and Sam Packer New developments in nuclear medicine.	Brookhaven National Laboratory	September 6, 1982
Feldman, Isaac Professor of Radiation Biology and Biophysics Uranium and polonium chemistry.	University of Rochester Medical Center	June 6, 1978
Fink, Kay Administration The polonium experiments at Rochester during World War II.	University of California, Los Angeles	February 8, 1979
Finkel, Asher Occupational Medicine (retired) The Argonne radium studies, chapter critiques.	American Medical Association Formerly Argonne National Laboratory.	October 9, 1981, with subsequent letters
Finkel, Miriam Biology Division (retired) The Met. Lab experiments on fission products and actinides. Postwar long-term experiments.	Argonne National Laboratory	September 6, 1978, October 9, 1981, with subsequent letters
Ford, Mary Internal emitter dosimetry.	Oak Ridge National Laboratory	April 17, 1979
Foreman, Harry, Professor Therapy for deposited radionuclides. Interview in San Diego.	University of Minnesota	1978
Foster, Richard Environmental Sciences Very broad. Early work at University of Washington and Hanford, especially aquatic biology. Pacific tests, whole-body counts, general environmental studies.	Battelle, Pacific Northwest Laboratories	June 11, 1979
Friedell, Hymer Professor of Radiology (retired) His book on history of Manhattan Project, old reports, work at WRU.	Western Reserve University	May 15, 1978, May 27, 1981

Name and Position	Institution	Date(s)
Goldman, Marvin Director, Laboratory for Energy Related Health Research General, emphasis on bone and experience at tests program at Laboratory, Chernobyl.	University of California, Davis	December 5, 1980, May 1983, and several informal follow-ups
Hacker, Bart Author of book in preparation on radiation protection at the weapons tests His book. Interview in San Diego.	Reynolds Electric and Engineering Co., Las Vegas	September 19, 1979
Hackett, P. L. and B. J. McClanahan Their programs.	Battelle, Pacific Northwest Laboratories	June 5, 1979
Haggerty, James Radium, chapter. Joint interview with C. W. Shilling and W. Lotz in Washington, June 1978.	American Red Cross, Washington Headquarters Formerly AEC	April 1978
Hansard, Sam History of the UT-AEC farm, and CARL programs.	Cooperative Animal Research Laboratory, Oak Ridge (formerly UT-AEC Experimental Farm)	April 18, 1979
Hasterlik, Robert The Argonne radium studies.	La Jolla Cancer Research Foundation, La Jolla, CA Formerly Argonne	April 28, 1980
Hempelmann, Louis Professor of Experimental Radiobiology (retired) The radium cases. The Los Alamos plutonium workers.	University of Rochester Medical Center	June 6, 1978, September 1981
Hewlett, Richard Historian (retired) Pertinent history of AEC.	AEC, ERDA, and DOE Headquarters, Washington.	March 15, 1979
Hodge, Harold Professor of Pharmacology and Toxicology (retired) Uranium research and inhalation toxicology, chapter reviews.	University of Rochester Medical Center University of California, San Francisco	October 25, 1980, and subsequent visits in California
Holaday, Duncan (retired) Uranium miner saga.	U.S. Public Health Service	July 9, 1979

Name and Position	Institution	Date(s)
Hull, Andrew Safety and Environmental Protection Division Radiation protection, environment studies.	Brookhaven National Laboratory	September 17, 1982
Hursh, John Professor of Radiation Biology and Biophysics (emeritus) Broad review of instrumentation, radium, polonium, and radon research.	University of Rochester Medical Center	May 31, 1978
Jee, Webster Professor, Radiobiology Program Utah programs, fallout, bone.	University of Utah	January 18, 1980
Jordan, Harry Work at NTS, particularly Project 56 and other plutonium safety tests.	Los Alamos National Laboratory	September 22, 1981
Kathren, Ronald Historians' views and experiences.	Battelle, Pacific Northwest Laboratories	June 5, 1979, and many subsequent discussions
Kornberg, Harry Manager (deceased) History of the Hanford biology effort and his experiences. General consideration of fallout and related problems, work with tritium.	Bonneville Power Administration and EPRI Formerly Hanford Biology Division	September 1, 2, 1982, with subsequent letters
Kreager, William (retired) NRDL.	U.S. Nuclear Regulatory Commission	December 6, 1979
Larson, Kermit UCLA work at NTS. Joint interview with Welander and Bonham.	Damson Moore, Seattle, WA	June 1, 1979
Lessard, Edward Safety and Environmental Protection Division Dosimetry of Marshalllese. Joint interview with Charles Meinhold part of the time.	Brookhaven National Laboratory	September 17, 1982
Lotz, William Inhalation Toxicology Programs of AEC. Also joint interview with Drs. Shilling and Haggerty, June 1978.	Electric Power Research Institute branch in Washington Formerly AEC Division of Biology and Medicine	March 15, 1979
Marks, Sidney Associate Manager, Biomedical and Environmental Research (retired) Broad review.	Battelle, Pacific Northwest Laboratories	June 11, 1979
Mays, Charles Professor, Radiation Biology Program Therapy for deposited radionuclides, the Utah experiments, Thorotrast.	University of Utah	January 18, 1980

Name and Position	Institution	Date(s)
McClellan, Roger Director His experiences at Hanford, development of the Lovelace program, general.	Inhalation Toxicology Research Institute, Lovelace Foundation, Albuquerque	September 26, 1981, and correspondence
McGrew, Thomas Environmental programs.	U.S. Department of Energy	April 4, 1980
Meinhold, Charles Head, Safety and Environmental Protection Division Broad aspects of program, special consideration of Marshallese dosimetry. Joint interview with Edward Lessard part of the time.	Brookhaven National Laboratory	September 17, 1982
Miller, Leon Professor of Radiation Biology and Biophysics and of Biochemistry (retired) History of tracer chemistry.	University of Rochester Medical Center	May 30, 1978
Morgan, Karl, Professor (retired) Formerly Head, Health Physics Division General, his career, radiation protection standards, research.	Georgia Institute of Technology Oak Ridge National Laboratory	April 20, 22, 1979
Morrow, Paul Professor Radiation Biology and Biophysics and of Pharmacology and Toxicology Analytical problems, work at Tennessee Eastman Corporation, industrial hygiene, inhalation toxicology and physiology.	University of Rochester Medical Center	June 1, 1978; and several subsequent discussions
Myers, William Professor of Radiology History of nuclear medicine.	Ohio State University	June 5, 1981
Neuman, William Professor of Radiation Biology and Biophysics (deceased) Uranium and bone, general plans, World War II work.	University of Rochester Medical Center	May 26, 1978
Noonan, Thomas Professor (retired) History of laboratory, early work with radioisotopes at the Univ. of Rochester.	Comparative Animal Research Laboratory, Oak Ridge (formerly UT-AEC Farm) University of Rochester Medical Center	April 18, 1979
Norris, William (retired) Bone seekers.	Argonne National Laboratory	September 7, 1978
Norwood, W. D. "Dag" Medical Officer (retired) Clinical management of radionuclide exposure cases, medical care of radiation workers.	Hanford Works (General Electric Company) Battelle, Pacific Northwest Laboratories	June 4, 1979

Name and Position	Institution	Date(s)
Osterburg, Charles Environmental programs.	U.S. Department of Energy	April 7, 1980
Palmer, Ray Whole-body counting. Joint interview with F. Cross.	Battelle, Pacific Northwest Laboratories	June 4, 1979
Palmiter, Claire (retired) Work of the Federal Radiation Council. First interview in San Diego.	U.S. Environmental Protection Agency Formerly Federal Radiation Council	November 11, 1978, April 2, 1985
Park, James Biology & Chemistry Dept. Experimental work with plutonium at Battelle.	Battelle, Pacific Northwest Laboratories	June 6, 1979
Parker, Herbert Former Manager and Staff Scientist (deceased) History of entire field with emphasis on early years.	Hanford Works (General Electric Company) Battelle, Pacific Northwest Laboratories	June 4, 1979
Ragan, Harvey Iodine experiment, fallout, pathology.	Battelle, Pacific Northwest Laboratories	June 8, 1979
Reynolds, Orr Executive Secretary General, and role of Office of Naval Research, radium chapter.	American Physiological Society	March 28, 1980
Richmond, Chester Associate Director His work at Los Alamos plus general overview.	Oak Ridge National Laboratory	April 18, 1979
Robertson, James Nuclear medicine, dosimetry. Interview at Toronto, Ontario, Canada.	Mayo Clinic Now DOE	May 15, 1978
Rohwer, Paul Health and Safety Research Division (now Head of Health Physics) Plowshare, Oak Ridge Environmental Program, assessment of former sites.	Oak Ridge National Laboratory	April 13, 1979, and subsequent corres- pondence and conferences
Romney, "Van" Professor The UCLA plant experiments and work at NTS.	University of California, Los Angeles	October 13, 1978, and subsequent visits
Ross, Donald Inhalation toxicology, industrial hygiene in AEC.	DOE Headquarters, Germantown	March 16, 1979, March 31, 1980
Ross, Joseph (deceased) UCLA programs, NTS involvement, control of data.	University of California, Los Angeles	October 13, 1978

Name and Position	Institution	Date(s)
Ross, Martha Oral history.	Bethesda, MD	April 7, 1980
Rothstein, A. Rochester uranium work.	Hospital for Sick Children Toronto, Ontario	May 17, 1978
Rundo, John Earlier work at Harwell, thorium, polonium, plutonium, radium, instrumentation. Interview at Lake Geneva, Wisconsin.	Argonne National Laboratory	October 15, 1981
Russell, William Biology Division Genetic studies with internal emitters. Joint interview with Dr. Cumming.	Oak Ridge National Laboratory	April 20, 1979
Sanders, Charles Biology & Chemistry Dept. His work with actinides.	Battelle, Pacific Northwest Laboratories	June 7, 1979
Schulte, Harry Research at Los Alamos; bioassay, industrial hygiene. Interview in San Diego.	Los Alamos Scientific Laboratory	March 22, 1980
Seaborg, Glenn Professor Former Chairman Chapters 6 and 7, history of actinides.	University of California, Berkeley U.S. Atomic Energy Commission	October 22, 1980
Seymour, Allyn Professor Aquatic biology programs, radioecology, Pacific and Alaskan tests, chapters 11-13.	University of Washington School of Fisheries	June 1, 1979, October 7, 1983, and letters
Shilling, Charles Executive Director Formerly Deputy Director, Division of Biology and Medicine Office of Naval Research, radium chapter, general operation of AEC programs.	Underwater Medical Assoc. AEC	June 7, 1978, March 28, 1980
Shoup, Sam (retired) Role of Oak Ridge Operations Office in internal emitter research. Puerto Rico.	Oak Ridge Operations Office AEC	April 10, 1979
Sikov, Melvin Embryo and fetus.	Battelle, Pacific Northwest Laboratories	June 6, 1979
Smith, Frank Associate Professor of Radiation Biology and Biophysics Uranium and fluoride work.	University of Rochester Medical Center	June 1, 1978
Smith, Victor Therapy for deposited radionuclides.	Battelle, Pacific Northwest Laboratories	June 7, 1979
Soldat, Joseph Internal emitter dosimetry, environmental transfer.	Battelle, Pacific Northwest Laboratories	June 7, 1979

Name and Position	Institution	Date(s)
Spiers, William Radiological physics, bone seekers, dosimetry. Interview in 1979 at Richland, Washington; in 1981 at Lake Geneva, Wisconsin.	United Kingdom	June 9, 1979, October 9, 1981
Sterner, James, Professor Medical Director Uranium and health problems of industrial hygiene in MED.	University of California, Irvine Eastman Kodak Company and Tennessee Eastman Corporation	April 7, 1978
Stover, Betsy, Professor Chapter 8, general philosophy.	University of North Carolina Formerly at University of Utah	December 7, 1980
Sullivan, Maurice Gastrointestinal transfer and toxicity on ingestion.	Battelle, Pacific Northwest Laboratories	June 6, 1979
Taplin, George (deceased) Nuclear medicine, UCLA work at NTS.	University of California, Los Angeles	February 7, 1979
Terrill, James USPHS (retired) Radium literature, role of PHS in internal emitter research.	Food and Drug Administration	April 4, 1980
Thomas, John Radiological physics, tracers.	University of Pennsylvania	July 12, 1979
Thomas, Robert Very broad.	Los Alamos National Laboratory, now Headquarters, DOE	September 22, 1981, and subsequent letters and visits
Thompson, Roy Perspective. History of Hanford and PNL program.	Battelle, Pacific Northwest Laboratories	June 8, 1979
Tobias, Cornelius, Professor Donner Laboratory Tracer chemistry, biophysics.	University of California, Berkeley	October 23, 1980
Tsivoglou, Ernest (retired at Decatur, Georgia) Radon measurements, the uranium miner's saga.	USPHS	April 11, 1979
Villforth, John Their history of PHS work in radiological health, general planning. Joint interview, in part, with James Terrill.	Food and Drug Administration	April 1, 1980
Voelz, George The plutonium workers and related measurements, epidemiology.	Los Alamos National Laboratory	September 23, 1981
Wald, Niel His career, clinical handling of radionuclide exposure cases, nuclear medicine.	University of Pittsburgh	July 10, 1979

Name and Position	Institution	Date(s)
Warren, Shields (deceased) History of nuclear medicine and of AEC biomedical programs. Interview at Toronto, Ontario, Canada.	Harvard University	May 19, 1978
Warren, Stafford (deceased) Chemical toxicology, Nevada and Pacific tests, history of MED.	University of California, Los Angeles	February 7, 1979
Welander, Arthur The UW program in aquatic biology. Joint interview with Bonham and Larson.	School of Fisheries, University of Washington	June 1, 1979
White, E. I. Environmental aspects.	GA Technology Now at National Council on Radiation Protection and Measurements	April 11, 1978, and subsequent conferences
Wilson, Robert Health and Safety Field tests, TG-57, Operation Roller Coaster, Idaho Falls tests, etc.	University of Rochester	June 6, 1978, and subsequent letters

Appendix B People and Places

A. General

This book goes to considerable lengths to describe the origin and development of specific projects and to name the people most concerned with them. This was especially true for what I have called the "king-sized experiments" and other major experiments, during and after World War II, at Argonne, Lovelace, Hanford, the Metallurgical Laboratory, Rochester, and Utah, among others. Nevertheless, a recapitulation of the American laboratories and the people whose work was quoted frequently may be useful; it is attempted in this Appendix.^(a)

Something of the milieu in which it all operated is also apparent in the text and in the preface. However, this book is by no means a history of the atomic energy effort in a broad sense. Hence, this Appendix is, except for citing a few useful general works, specific to the people and places discussed in the book.

B. Pre-World War II

The sites most involved with the biomedical problems of radioactivity in the earlier years are apparent in the four chapters on natural radioactivity (chapters 1 through 4) and in chapter 5 that deals, in part, with accelerators and accelerator-produced radionuclides. It was an international effort.

As is clear from chapter 3, the earliest research and clinical investigations occurred over more than a century before the discovery of radioactivity and were in connection with the health problems of miners. This was concentrated in Europe, particularly Germany and Czechoslovakia, as described in some detail in that chapter. There was much less activity on the uranium miner problems in the United States, although other facets, such as pneumoconiosis, effects of silica and of toxic gases, received considerable attention during the pre-World War II years in other types of mines.

(a) Remember our scope did not allow for in-depth discussions of the organization and operation of laboratories abroad, even though their work is quoted frequently.

The problems of the luminous dial painters, radium chemists, and radium patients were, by contrast, very actively under study in the United States. This centered at Massachusetts Institute of Technology (MIT) under R. D. Evans and colleagues as described in detail in chapter 1. There were significant but lesser contributions from the U.S. Public Health Service (PHS) among others.^(a)

During the decade of the 1930s, almost every major accelerator (cyclotron) had at least some involvement with biology and medicine. Most actively engaged were those at Berkeley (John Lawrence, Joseph Hamilton, and colleagues); MIT-Massachusetts General Hospital (MGH) (Robley Evans, Joseph Aub, Arthur Roberts, and colleagues); Rochester (William Bale, Wallace Fenn, Lee Du Bridge, S. Barnes, Paul Hahn, George Whipple, and colleagues); and Washington University, St. Louis (Arthur Compton, A. H. Allison, and colleagues, and later, Martin Kamen). The laboratories at Berkeley and MIT-MGH were the furthest into research leading to the discoveries of the 1940s in biomedical science, but all were into tracer chemistry and radiochemistry. Much that led later into the field of nuclear medicine was begun in those prewar facilities and by those pioneers. As described in chapter 5, the collaboration of biologists, physicians, and physicists was essential and became highly developed in those days.

C. Period of World War II (The Manhattan District-MED)

The giant of this period, for our purposes, was the Metallurgical Laboratory based in Chicago. Since most of the Berkeley work was reported in Metallurgical Laboratory reports, the giant can be said to have had his feet firmly planted in both Illinois and California. The biomedical program was presided over by Robert S. Stone, a radiologist from San Francisco, with major direction from MED Headquarters Medical Division, viz., Stafford L. Warren and his deputy Hymer Friedell.

The Chicago biomedical group was headed in part by K. C. Cole with Raymond Zirkle in biophysics; with the radioisotope toxicology aspects in the hands of R. Abrams, D. S. Anthony, E. S. G. Barron, R. D. Finkle, L. O. Jacobson, Walter Kisielecki, H. Lisco, J. J. Nickson, William Norris, C. L. Prosser, E. R. Russell, T. P. Singer, and Albert Tannenbaum; and with systematic histopathology presided over by William Bloom. In the later years, Miriam P. Finkel and Jack Schubert joined and continued well into the postwar years.

A portion of the Chicago Met Lab work utilized external radiation sources, but a surprisingly large part of their biomedical effort involved radionuclides. This was undoubtedly in part because the major physicochemical activities with plutonium and the other transuranium elements, under Glenn Seaborg and his associates, were going on close by.^(b)

The group at Berkeley, which reported as part of the Metallurgical Laboratory, was, of course, dominated by Joseph Hamilton, but there was a capable

(a) The role of the PHS in studies of radium and those individuals who had received radium extends well beyond that described in chapter 1. A book on the history of the PHS's involvement with radiation matters by James Terrill, still in preparation (personal interview 1980), should spell this out more completely.

(b) These were not in the same building, and they were separated by the stringent security restrictions of the day as well as by a few city blocks. Nevertheless, the chemistry group and biologists knew what was important.

cadre of colleagues such as Kenneth Scott, Dorothy Axelrod, Harold Copp, J. Crowley, and Lester Van Middlesworth. These were joined in the later years by Patricia Wallace, who later became Patricia Wallace Durbin and who is still carrying forward internal emitter research at Berkeley. Unfortunately, nearly all of the others scattered into other fields at the end of World War II, and Joe Hamilton died of leukemia at too young an age.

As at Chicago, there was other radiation work. This was in the sphere of Ernest and John Lawrence and in the Donner Laboratory, and the Virus Laboratory with which we associate names such as Cornelius Tobias, Hardin Jones, Melvin Calvin, Lowry Dobson, and others.

A second major center for biomedical research under the MED, separate from the Met Lab, was the University of Rochester Atomic Energy Project at the University of Rochester School of Medicine and Dentistry in Rochester, New York.^(a) Of the three divisions of the project, Biophysics, Medical, and Pharmacology, headed respectively by W. F. Bale, J. W. Howland, and H. C. Hodge, major internal emitter research occurred in two. The enormous enterprise with natural uranium, described in chapters 2 and 9, was in the Pharmacology Division. The work with polonium, plutonium, and radium was centered in the Biophysics Division. Both of these resulted in major postwar monographs. In the Pharmacology Division, much depended on the scientific acumen and dedication of people like A. L. Dounce, W. F. Neuman, A. Rothstein, H. Stokinger, and others, while in the Biophysics Division principal figures besides W. F. Bale were G. Boyd, G. Casarett, R. Fink, R. Metcalf, H. Silberstein, G. Suter, and colleagues, with tissue pathology presided over later by G. W. Casarett. The Rochester Atomic Energy Project was directed, during most of the war years, by Andrew Dowdy from the Department of Radiology.

There was also a large effort at Rochester with external radiation sources. Particular mention should be made of a large mouse genetics program under the direction of Donald R. Charles. This program, while it had problems with infections, etc., can be regarded as a forerunner of the "megamouse" experiment done in the postwar years at Oak Ridge.

As described in chapters 2, 8, and 9, Rochester used the inhalation route for many of its exposures to uranium and, to a lesser extent, other radionuclides. It became, and has continued to be, a center for inhalation toxicology.

The Los Alamos Scientific Laboratory was not into biomedical research during the war years, as is described in the text. They were heavily involved in bioassay and health protection. Key figures were Dr. Louis Hempelmann and later Wright Langham.

The key studies in aquatic biology at the University of Washington and at Hanford constituted a third center. These have been described in so much detail in the environment chapters (11 through 15) that little more needs to be added here. We will always remember the names Kelshaw Bonham, Lauren Donaldson, Allyn Seymour, Arthur Welander, and others at Seattle, and Richard Foster and his colleagues at Hanford.

Before we conclude this brief recapitulation of people and places of specific import to the subject matter of this book during the war years, a few of the

(a) The Medical Director of the MED, Stafford L. Warren, was Professor of Radiology at Rochester and knew the staff and the potential well enough to place the second major biomedical activity there.

general discussions of the wartime effort should be noted, since these might give the reader a broader overview of the milieu in which the research was done. Those cited are a few of many. They are listed in chronological order of publication; all are postwar, but are primarily about the war years.

Baxter, J. P. III. 1946. *Scientists against time*. (OSRD History). Cambridge, Mass.: MIT Press.

Fermi, L. 1954. *Atoms in the family—My life with Enrico Fermi*. Chicago: Univ. of Chicago Press.

Compton, A. H. 1956. *Atomic quest—A personal narrative*. Oxford, England: Oxford Univ. Press.

Lapp, R. 1956. *Atoms and people*. New York: Harper Brothers.

Byrnes, J. 1958. *All in one lifetime*. New York: Harper Brothers.

Lawrence, W. L. 1959. *Men and atoms*. New York: Simon & Schuster.

Strauss, L. L. 1962. *Men and decisions*. (Contains both wartime and postwar aspects.) Garden City, N.Y.: Doubleday and Company, Inc.

Groves, L. R. 1962. *Now it can be told*. New York: Harper Brothers.

Seaborg, G. T. 1963. *Man-made transuranium elements*. (Includes some early postwar works.) Englewood Cliffs, N.J.: Prentice-Hall, Inc.

Warren, Stafford. 1966. Part VII in *Radiology in World War II*. Washington, D.C.: Office of the Surgeon General, Department of the Army.

Cave Brown, A. and C. B. MacDonald, eds. 1977. *The secret history of the atomic bomb*. New York: The Dial Press/James Wade.

Libby, L. M. 1979. *The uranium people*. Crane Russak, New York: Charles Scribner & Sons.

Weart, S. R. and G. W. Szilard, eds. 1979. *Leo Szilard: His version of the facts*. Holliday Lithograph Corporation.

Rhodes, R. 1986. *The making of the atomic bomb*. New York: Simon & Schuster.

Hacker, B. C. 1987. *The dragon's tail—Radiation safety in the Manhattan Project, 1942-1946*. Berkeley, Calif.: Univ. of Calif. Press.

D. The Post-World-War-II Years

The principal sites and people of this era of biomedical research with radio-nuclides have been taken up in depth (chapters 1, 2, 3, 4, 8, 9, 10, 11-15, 19, 20) sufficient to make only general comments necessary here.

Brookhaven

Brookhaven National Laboratory (BNL) was entirely a postwar creation. Biomedical work has thrived in the very strong medical division; in the earlier years in a strong botany program that was both basic and applied; and in terms of environmental contamination, including recently the dosimetry for the exposed Marshall Islanders in what was the Health Physics Division and is now the Safety and Environmental Protection Division.

The Medical Division was originally headed by Lee Farr whose interests in neutron capture therapy with uranium we saw in chapter 2. For many years it was headed by Victor Bond, a broad-gauge radiation biologist and physician. Associated with the Division have been the physicians Eugene Cronkite and

Robert Conard, who have had more to do with the care and investigation of the Marshall Islanders than any other individuals.^(a) Stanton Cohn has operated an important program in mineral metabolism using the whole-body counter. Other BNL people can be seen in the interview listing of Appendix A (e.g., Carsten, Cowan, Hull, Lessard, Meinhold).

At the cellular level, Drs. Bond, Carsten, Cronkite, and others, produced detailed investigations of microdosimetry with tritium and other low energy beta emitters. Particular emphasis was placed on the troubling problem of possible transmutation effects.

The laboratory and field experiments with plants concerned largely external radiation sources. They are not described in any detail in this book, but we should note that Arnold Sparrow and his wife Rhoda developed a bona fide center for radiation botany.

Brookhaven has a medical reactor and access to many other sources of external radiation and has recently added a program in inhalation toxicology.

Chicago

The former Met Lab facility moved from the University of Chicago campus to the Le Mont site of the Argonne National Laboratory. The director of the Biology Division for the majority of the postwar years of significance to this book was Austin M. Brues, who had had early experience with radium (see chapter 1). Miriam Finkel continued long-term studies with many colleagues, and her husband, Asher Finkel, joined the Argonne Radium Studies along with Robert Hasterlik, Charles Miller, and others. William P. Norris continued his work on bone seekers, partly in collaboration with Walter Kisielewski; M. White Rosenthal and Arthur Lindenbaum engaged in definitive studies of the role of chemical state on the metabolism of radionuclides; Jack Schubert did his pioneer work with radiocolloids and the therapeutic removal of radionuclides; John Marshall developed his model for alkaline earth metabolism in bone; Henry Lucas and Andrew Stehney followed out radium and radon problems; Douglas Grahn looked into genetic effects of deposited radionuclides; among other things; and in later years, John Rundo, A. T. Keane, R. E. Toohey, M. H. Bhattacharyya, and R. P. Larsen^(b) joined the roster.

In addition to the Biology Division, there was a Radiological Physics Division, headed by Leo Marinelli, which made many contributions to the internal emitter field.

In the late 1960s, the Center for Human Radiobiology was developed at Argonne, as described in chapter 1. This was directed by Robert Rowland and included many former members of the Biology Division (e.g., Schlenker, Brues, Marshall, Stehney, Lucas, P. Failla, Holtzman, Keane).

As noted in chapter 1, the Argonne Cancer Research Hospital (ACRH) was built by the Atomic Energy Commission (AEC) near the University of Chicago Medical School. It assimilated several key investigators from the MED days and provided very important clinical facilities and expertise for the Argonne Radium Studies, as well as for other phases of work on radiation effects. Names to

(a) They also did work in many other fields. Cronkite, for example, is well-known as a hematologist.

(b) Remember these are limited to those working with radionuclides more or less full time.

remember especially are Leon O. Jacobson, Lawrence H. Lanzl,^(a) and colleagues. In still later years (1970s), the ACRH became the Franklin McLean Memorial Institute of the University of Chicago, but it has since lost some of its identity.

Hanford—Pacific Northwest Laboratory

The postwar development of Hanford is traced in chapters 8, 9, 11 through 15, and 19. The blossoming of a first-class biology program from what had been largely a monitoring and control operation is due to the foresight and persistence of Herbert M. Parker, the wartime manager of the health aspects of the plutonium production operation, who became postwar manager of the entire Hanford facility. The first manager of the Biology Division was Harry Kornberg. He did important research on tritium, on plants, and in other areas, some of it in collaboration with R. C. Thompson, who has remained a pillar of the radio-nuclide community ever since. Leo Bustad operated a series of important long-term experiments until his departure to the University of California at Davis. W. J. Bair became manager of what was called the Pharmacology Operation and developed an outstanding program in inhalation toxicology with the many colleagues named in chapter 9. This operation is still under way, although Dr. Bair has become manager of a large portion of the entire biomedical effort of the successor to the Hanford laboratory, Pacific Northwest Laboratory (operated by Battelle Memorial Institute). The laboratory research was augmented by many others, such as Fred Cross, Pat Hackett, B. J. McClanahan, Jim Park, Harvey Ragan, Chuck Sanders, Mel Sikov, Victor Smith, Bruce Wachholz, and others named in Appendix A.

Meanwhile, the medical aspects were guarded by W. D. "Dag" Norwood in a manner that led to the eventual development of the Hanford Environmental Health Foundation, which now manages the U.S. Transuranium and Uranium Registries.

The environmental work continued under Richard Foster with a series of notable colleagues such as Wayne Hanson. In more recent years, it was managed by Burton E. Vaughan, in close association with Ray Wildung, et al.

Like many other laboratories of the AEC era, the Battelle group has now diversified into many nonnuclear areas but is applying the same basic research techniques with emphasis on mechanisms.

Health and Safety Laboratory (HASL)^(b)

This group was an operational arm of the AEC. It developed around the problems of industrial hygiene and bioassay for uranium, supplied major aid to the PHS regarding the uranium miner and miller problems in the western states, was a center for measurements (in the thousands) and ideas during the entire fallout controversy, and has continued under the Energy Research and Development Administration (ERDA) and the Department of Energy (DOE) as the Environmental Measurements Laboratory. Most of the experiments around problems of the postwar years have been improved and advanced by contributions of equipment, know-how, and/or ideas from HASL. Their contributions to the fallout work were enormous and done "in house."

(a) Dr. Lanzl very kindly supplied a picture of the ACRH and a full history that unfortunately we could not include in detail here.

(b) Now Environmental Measurements Laboratory.

In its earlier days, the Laboratory was directed by Merrill Eisenbud who later went to New York University. John Harley then became director. Key figures in the group for internal emitter work were Roy Albert, A. J. Breslin, E. P. Hardy, Jr., J. H. Harley, N. Harley, P. W. Krey, James McLaughlin, J. Rivera, H. Spencer, H. L. Volchok, and G. A. Welford, among others.

Lawrence Livermore Laboratory

Like Brookhaven, the Lawrence Livermore National Laboratory was entirely a postwar creation. As noted in the environment chapters (11 through 15), the biomedical program was developed to attack problems of environmental contamination, especially fallout and aspects of Project Plowshare. The principal names to be noted are: Lynn Anspaugh, Y. C. Ng, V. E. Noshkin, W. L. Robison, and colleagues. The laboratory is now proceeding on a very broad front. Edward Teller was the original director.

Los Alamos

As described in chapters 7, 8, 16, 19, and elsewhere, Los Alamos Scientific Laboratory (later Los Alamos National Laboratory) did not have a formal biomedical program during the war. It did have much interest in bioassay problems. The postwar activities developed rapidly and were led primarily by Thomas Shipman, with carry-over help from Louis Hempelmann,^(a) and after him, George Voelz, on the medical side, and on the laboratory side by Wright Langham, plus a strong corps of colleagues such as R. E. Carter, P. N. Dean, H. Foreman, J. E. Furchner, J. Healy, Harry Jordan, J. E. London, J. McInroy, W. Moss, E. A. Pinson, Chester Richmond, John Storer, Agnes Stroud, and more recently, R. G. Thomas. Wright Langham was a towering figure in the field of radionuclide metabolism and effects, both pre- and postwar. He grew up with plutonium, and much of his interest was centered on it and other actinides—enough so that he would early be called “Mr. Plutonium” of the biomedical world. However, he also had keen interests in fallout, standard setting, etc. Indeed, there were few areas of the internal emitter field into which he did not have significant input. In later years, the Los Alamos group broadened considerably into molecular radiobiology. There was also a strong industrial hygiene operation under the direction of Harry Schulte.

Lovelace

The development of the Inhalation Toxicology Research Institute (ITRI) at the Lovelace Foundation in Albuquerque and its principal people are described in depth in chapters 8 and 9. After initial direction by R. Lovelace and C. S. White, with capable assistance from R. G. Thomas, T. Mercer, J. K. Scott, and others, the management went to Roger McClellan, formerly of Hanford and AEC Headquarters. With a strong team made up of individuals like Bruce Boecker, A. Brooks, Fletcher Hahn, C. H. Hobbs, R. Jones, George Kanappily, J. A. Mewhinney, Bruce Muggenburg, H. C. Yeh, and others, ITRI has become, along with Battelle, one of the strongest centers in the world for inhalation toxicology. Almost all of its earlier work concerned radionuclides. They are now into a large variety of energy-related inhalation and conventional toxicological investigations.

(a) Hempelmann was by then at the University of Rochester. However, he played a key role in medical care of the Los Alamos workers during the war and continued actively in the follow-up studies on the plutonium workers.

Massachusetts Institute of Technology

During the post World War II period, the so-called Radioactivity Center at MIT continued to be the center for studies on radium in humans, except for the group at Argonne National Laboratory doing the Argonne Radium Studies (chapter 1), and (to a lesser extent) radon and the uranium miner problems. The project leader was still Robley D. Evans, who continued to surround himself with competent colleagues and students, such as C. J. Maletskos, R. A. Dudley, R. Schlenker, M. M. Shanahan, N. C. Telles, and others. There were regular and detailed annual reports that included full medical data on the persons whose body burdens of radium and related isotopes had been determined during that year. There were also regular open literature publications from this consistently active group, which merged in 1970 into the Center for Human Radiobiology at Argonne National Laboratory. As always, collaboration between physical and biological scientists was emphasized.

Oak Ridge

The high quality biology program at Oak Ridge National Laboratory (ORNL) developed by Alexander Hollaender eschewed internal emitter research, except for some relatively recent forays by William Russell and his colleagues into genetic effects of deposited radionuclides. This is being done partly in collaboration with Argonne National Laboratory (Douglas Grahn).

The Health Physics Division at Oak Ridge did not carry out large amounts of conventional laboratory research with animals, although B. Fish and colleagues did some work with uranium. On the other hand, the Division became the world center for internal emitter dosimetry. Walter Snyder (now deceased) was the towering figure in this effort, with the Division Head, Karl Z. Morgan, supplying encouragement and advice. The capable and patient hands of Mary Rose Ford and Mary Jane Cook made an enormous difference in the output of this group. Also, Isabel Tipton carried out important work on trace elements in human tissues in her laboratory at the University of Tennessee, under Oak Ridge support. In later years, John Auxier added to the internal emitter activities, while John Poston and Keith Eckerman became associated with the internal dosimetry effort and its relationships to Medical Internal Radiation Dose (MIRD). Chester Richmond moved over from Los Alamos to assume a high administrative post at ORNL, but kept his interest in radionuclide research.

The University of Tennessee-Atomic Energy Commission Farm, later CARL, is described in detail in chapter 13 (Cycil Comar, F. W. Lengemann, R. Wasserman, T. Noonan, et al.).

University of California, Berkeley—Lawrence Radiation Laboratory

With the dismantling of the "medical cyclotron" and razing of the Crocker Laboratory (see chapter 6), the internal emitter activities went to a site above the campus, part of the Lawrence Radiation Laboratory, and are represented in the postwar years primarily by Patricia Durbin and colleagues. The work is cited in extenso in chapters 8, 16, 19, and elsewhere.

University of California, Davis

The story of the development of this program is given in detail in chapter 8 and its findings in chapter 13. In the early postwar years, a beagle colony was

developed under the leadership of A. C. "Bud" Anderson. It concerned effects of external radiation.

When the need to develop a "king-sized experiment" around the problems of ingested strontium as part of the fallout activities arose, the Davis campus became the site. Shortly it came under the direction of Leo K. Bustad, who came to Davis from Hanford and remained for many years. When Bustad went to his alma mater, Washington State University, as dean of the School of Veterinary Medicine, Marv Goldman, his colleague and University of Rochester graduate, succeeded him as director. It was known as the Radiobiology Laboratory until diversification prompted a name change to "Laboratory of Energy Related Health Research." Names to remember besides Bustad and Goldman, are R. J. Della Rosa, S. Book, L. S. Rosenblatt, M. H. Momeni, R. R. Pool, N. J. Parks, and O. Raabe, after his transfer from Lovelace.

University of California, Los Angeles (UCLA)

The UCLA project grew de novo directly after the war as sort of a clone to the Rochester project. When Stafford Warren left the MED post to become dean of the new Medical School at UCLA, he wanted to keep his finger in the atomic energy field. He was enabled to do so by having the AEC support a project on the campus somewhat akin to the Rochester Project that he squired in MED days. It participated especially actively in the weapons testing program. Some of the people concerned were A. W. Bellamy, M. Greenfield, Kermit Larson, H. M. Mook, J. W. Neel, H. Nishita, J. H. Olafson, "Van" Romney, and A. Wallace. Some of these have spent most of their careers on the ecological and other aspects of fallout with correlated laboratory experiments. Others (Taplin, Bennett, Riley) worked into various aspects of nuclear medicine and drifted away in part from the project to the Radiology Department. The work of the former group is seen most in the environment chapters (11 through 15) and of the latter group, in the ones on nuclear medicine (20) and inhalation toxicology (9, 10).

University of Rochester

After World War II, the University of Rochester Atomic Energy Project became an academic department of the medical school, viz., Radiation Biology, then Radiation Biology and Biophysics. Many of the key figures from the wartime research remained, and the programs continued, but with more fundamental overtones. Those remaining included G. Casarett, K. Lauterbach, Paul Morrow, William Neuman, Aser Rothstein, as well as the division heads named earlier (Bale, Hodge, Howland). John B. Hursh returned to Rochester from the Radiation Laboratory at MIT. J. N. Stannard returned from war duties at the National Institute of Health and in the U.S. Navy. The extension of the uranium work under H. C. Hodge, with help from L. Leach and others, is described in chapter 2. The continuation of the work with alpha emitters, radium, radon, and polonium, by Hursh; polonium and inhalation toxicology by Stannard and colleagues L. Casarett, Mercer, Morken, Morrow, Smith, Thomas, Wilson, are described in chapters 1, 4, 9, and 14.

The basic contributions of Neuman and Rothstein are highlighted in chapter 21, along with other such contributions from the Rochester group. G. W. Casarett, whose name we saw in the MED work from Rochester, for many years continued the polonium research he was associated with for his doctoral thesis,

but later became involved with general radiation pathology, radiology, and large animal experiments with external radiation.

The postwar Rochester project did much more than the internal emitter research and inhalation toxicology described in this book. It was a center for graduate education in the new field of atomic energy as applied to biology and medicine. It was this author's privilege to spearhead this effort. Rochester also carried out much basic research in cellular radiobiology and general biophysics.

Many of the AEC laboratories were requested to participate in the weapons testing program. Except for UCLA, Rochester seems to have contributed as much or more in manpower and equipment as any of the major projects, well beyond the National Laboratories (see especially Wilson and Thomas).

Finally, Dr. Hodge's pharmacology division became the first line of defense for AEC in general toxicology. Whenever a new substance or process with potential toxicologic aspects came to light, the AEC would ask Rochester to get an initial reading on the substance or process, whether chemical or radioactive. It was traditional for the request to arrive on Friday, with a preliminary answer expected by the next week!

As a project at first associated physically and administratively with a major medical school, the Rochester group was probably one of the most academically oriented ones. Yet, it took part in many very practical enterprises.

The director for many years was Dr. Henry A. Blair, a physicist turned biophysicist and radiation biologist who made significant contributions to the analysis of life-span shortening by radionuclides and by external radiation.

University of Utah

The first of the "king-sized experiments" with radionuclides was developed in the Department of Anatomy at the University of Utah Medical School in Salt Lake City. It is described in detail in chapter 9, including the "founding fathers" and the influence of John Z. Bowles, dean of the school. It has been and remains a key laboratory in internal emitter research. Names to remember are J. Arnold, D. R. Atherton, F. W. Bruenger, T. and J. Dougherty, W. S. S. Jee, R. D. Lloyd, C. W. Mays, J. E. Rehfeld, W. Stevens, B. J. Stover, G. N. Taylor; and, in recent years, M. E. Wrenn.

Others

There were many other laboratories that developed *de novo* after the war that had significant involvement with "internal emitters." Examples are the Armed Forces Radiobiology Laboratory in Bethesda;^(a) the Naval Radiological Defense Laboratory in San Francisco; the University of Tennessee-AEC Experimental Farm in Oak Ridge; the Laboratory of Physical Biology at Cornell University; the Mound Laboratory at Miamisburg, Ohio, which had a program with polonium for a few years; the Public Health Service Laboratories in Nevada, Alabama, Massachusetts, and Maryland, etc. Each of these is described in sufficient detail in the text to make further exposition here redundant. The Armed Forces Institute program embraced mostly external radiation problems.

(a) This organization was set up at about the time of the demise of the Naval Radiological Defense Laboratory. It had a much more limited program with primary emphasis for many years on effects of high doses of external radiation on behavior and performance. There was not much work in the radionuclide field. In later years, the laboratory developed the diversified programs in molecular radiobiology and related areas.

Finally, the "king-sized" experiments at Hanford, Utah, University of California at Davis, and at Lovelace (ITRI) were described in full detail in chapters 8, 9, and 13. The reader is referred to those expositions for the full story.

General Literature

The early postwar years easily became the subject of personal narratives or periodic reviews, something like those described in part C of this Appendix. Among these are books on the development and history of the AEC, a unique administrative structure within our government, the Atoms for Peace Program, and miscellaneous biographies. A few are listed below.

Hewlett, R. G. and O. E. Anderson, Jr. 1962. *The new world. 1939/1946*. Volume I of a history of the United States Atomic Energy Commission. University Park, Pa.: Penn State Univ. Press.

Hewlett, R. G. and F. Duncan. 1969. *Atomic shield. 1947/1952*. Volume II of a history of the United States Atomic Energy Commission. University Park, Pa.: Penn State Univ. Press.

Allardice, C. and E. R. Trapnell. 1974. *The Atomic Energy Commission*. The Praeger Library of U.S. Government Departments and Agencies. New York-Washington: Praeger Publishers.

Fermi, L. 1957. *Atoms for the world—United States participation in the conference on the peaceful uses of atomic energy*. Chicago: Univ. of Chicago Press.

Lawrence, J. H., ed. 1965. *Progress in atomic medicine*. Volume 1 of several volumes. New York-London: Grune & Stratton.

Childs, H. 1968. *An American genius—The life of Ernest Orlando Lawrence*. New York: E. P. Dutton & Co., Inc.

Seaborg, G. T. 1972. *Nuclear milestones—A collection of speeches*. San Francisco: W. H. Freeman and Company.

Kathren, R. L. and P. L. Ziemer, eds. 1980. *Health physics: A backward glance*. New York-Oxford: Pergamon Press.

Strauss, L. Later chapters in the book cited in part C of this Appendix.

Hacker, B. C. 1987. *The dragon's tail—Radiation safety in the Manhattan Project, 1942-1946*. Berkeley, Calif.: Univ. of California Press.

Note

All names of authors and individuals otherwise referred to in the text have been placed in Index I. This is called "People," since not all individuals were cited by virtue of being an author. It is hoped that this rather extensive listing will be used to extend and amplify the rather cryptic references possible in this Appendix. A separate index (Index II) was prepared to permit searching for specific institutions or organizations. This should be used to flesh out the details of institutions and organizations cited in this Appendix and to add to the cadre that was, perforce, truncated here.

Appendix C

The National Nuclear Energy Series (NNEs) Hiatus

Throughout the review of the Manhattan Engineering District (MED) work of the World-War-II period, we had numerous occasions to refer to and to review, in part, a series of Metallurgical Laboratory reports referred to cryptically as the "NNEs Hiatus." This set of fifty documents (originally labeled "PPR" for Plutonium Project Reports), many of them in several sections of considerable length, was intended for publication as volumes 22F, 22G, and 22H of Division IV of the NNEs, the monumental postwar monograph series on the work of the MED. Volumes 22F-H were never published because of the upheavals in personnel and planning during the early postwar years when the NNEs volumes were being assembled, and because of the need for the designated editor for the Chicago volumes, Raymond E. Zirkle, to concentrate on other volumes for which he had manuscripts in hand. Why these particular manuscripts were never received by McGraw-Hill or the NNEs editorial board is not clear.^(a) Most of the papers had appeared in the report literature, classified in the beginning, and were gradually declassified. A few were published eventually in the open literature, but the organized progression envisioned for the volumes was lost. For this reason, the titles and MDDC report number, if available, and a few other details are given in this Appendix for the fifty papers planned, along with a quick summary of the NNEs.

Many of the reports were available in this author's files from years of careful accumulation or were obtained from DOE archives, the capacious files of Dr. Patricia Durbin at Berkeley, and other friends with saving habits such as Hymer Friedell at Case-Western Reserve University. Some of the most important and/or comprehensive reports that had very little postwar distribution are reviewed in some depth in the pertinent chapters of this book. Indeed, this feature was one of the original reasons behind writing the book.

(a) Many of the reports were not very polished, many had significant gaps that the authors undoubtedly hoped to fill. In other cases, the authors had already turned to other things, returned to their home institutions, or otherwise found it nearly impossible to reach back to finish the revisions needed for publication.

Also, courtesy of Dr. Durbin, this author was able to see and use abstracts from Nuclear Science Abstracts of many of the reports for which he could not obtain full copies. Referral to these abstracts and the "CH" number corresponding to the MDDC number are being kept on file by the author and will be supplied to interested readers on request, to the extent possible. Abstracts are not included here since this would overlap, unduly, the discussions in the text.

I am especially grateful to Dr. Durbin for her help in tracking down this material. My task was eased because she had already gathered many items, including a letter from William Vaden, Deputy Extension Manager of the AEC Division of Technical Information Extension, Oak Ridge, to Dr. R. K. Wakerling, Technical Information Division at Lawrence Radiation Laboratory, dated November 30, 1967, that enclosed the master listing.

List of Reports in the "NNES Hiatus"
(Volumes 22F, G, and H of the National Nuclear Energy Series)

Intended General Title: Metabolism and Biological Effects of Internal Emitters

Intended Running Title: Part V. Radiobiology Collected Papers

Paper No.	Title(a) and Authors	Report No.
1.	Preparation of Fission Products for Use in the Experimental Biology Section By A. Broido	MDDC-1244
2.	Methods of Analysis of Fission Products in the Experimental Biology Section By P. C. Tompkins, A. Broido, and L. Wish	MDDC-616
3.	The Quantitative Estimation of the Activity of Beta particle Emitters By A. Broido, J. Teresi, and P. Tompkins	MDDC-598
4.	Methods for the Quantification of Radium By P. C. Tompkins, W. P. Norris, L. Wish, and R. D. Finkle	MDDC-699
5.	The Handling of Radioactive Materials in the Experimental Biology Section By P. C. Tompkins, A. Broido, and J. D. Teresi	MDDC-377
6.	An Improved Method for Cutting Undecalcified Bone Sections and its Application to Radio-autography(b) By D. J. Axelrod	MDDC-450
7.	Calculations of Dosage Due to Internal Emitters(b) By W. Cohn	No Number
8.	The Metabolism of Carrier-free Fission Products in the Rat By K. G. Scott, R. Overstreet, L. Jacobson, and J. G. Hamilton	MDDC-1275
9.	Radiotoxicity of Injected Sr ⁸⁹ for Rats, Mice, and Rabbits I. Introduction: Methods By D. Anthony, K. Lathrop, and R. Finkle	MDDC-1540
	II. Metabolism and Organ Distribution By D. Anthony, K. Lathrop, and R. Finkle	MDDC-1363

Paper No.	Title(a)	Report No.
	III. Lethal Action and Clinical Changes By D. S. Anthony, K. Lathrop, and R. H. Snyder	MDDC-1364
	IV. The Hematological Effects of Enterally and Parenterally Administered Strontium-89 in Mammals By E. L. Simmons and L. O. Jacobson	MDDC-1387
10.	Acute Radiotoxicity of (Ba-La) ¹⁴⁰ in Rats and Mice	
	I. Preparation and Administration of the Emitters By R. D. Finkle, R. H. Snyder, and P. C. Tompkins	MDDC-1248
	II. Metabolism of (Ba-La) ¹⁴⁰ By R. H. Snyder, W. E. Kisieleski, D. S. Anthony, and R. D. Finkle	MDDC-1279
	III. Effects on Weight and Food Intake of Animals Treated with (Ba-La) ¹⁴⁰ By R. H. Snyder, G. A. Sacher, and J. D. Teresi	MDDC-1343
	IV. Lethal Action and Clinical Symptoms By R. D. Finkle, R. H. Snyder, and W. E. Kisieleski	MDDC-1207
	V. The Effect of (Ba-La) ¹⁴⁰ on the Hematological Constituents of the Peripheral Blood of Rats and Mice By L. O. Jacobson	MDDC-1261
11.	Acute Radiotoxicity of Injected Cesium-144 in the Rat By D. S. Anthony and K. A. Lathrop	MDDC-1326
12.	Acute Radiotoxicity of Injected Yttrium-91 By D. S. Anthony	MDDC-1240
13.	Acute Radiotoxicity of Injected P ³² in Mice I. Metabolism and Survival By D. S. Anthony and R. H. Snyder	MDDC-881
14.	The Deposition of Plutonium and Certain Fission Products in Bone as a Decontamination Problem	AECD-2483
	I. Factors Affecting the Absorption of Radioactive Strontium from the Gut By D. H. Copp, D. M. Greenberg, and J. G. Hamilton	(c)
	II. Factors Affecting the Retention of Injected Radioactive Strontium By D. H. Copp, D. M. Greenberg, and J. G. Hamilton	(c)
	III. Effect of Age and Dietary Calcium on Radioactive Sr, Y, Ce, and Pu By D. H. Copp, M. J. Chace, and J. G. Hamilton	(c)
	IV. Effect of Treatment on Chronic Elimination of Radioactive Sr, Y, Ce, and Pu By D. H. Copp, L. Van Middlesworth, E. M. Cuthbertson, M. J. Chace, and J. G. Hamilton	(c)
	V. Uptake of Radioactive Sr, Y, and Pu in Healing Fracture Callus By L. Van Middlesworth, D. H. Copp, and J. G. Hamilton	(c)
	VI. Effects of Severe Phosphorus Deficiency By D. H. Copp, M. J. Chace, and J. G. Hamilton	(c)
	VII. Bone Radioautographs of Radioactive Sr, Y, Ce, Zr, and Pu By Dorothy Axelrod, D. H. Copp, and J. G. Hamilton	(c)

Paper No.	Title ^(a) and Authors	Report No.
15.	Production and Analysis of Radioactive Aerosols By E. Abrams, A. M. Potts, C. E. Beilman, I. Wender, W. Lohr, S. Postel, and L. L. Forker	MDDC-795
16.	Metabolism of Inhaled Fission Product Aerosols By R. Abrams, H. C. Seibert, A. M. Potts, W. Lohr, and S. Postel	MDDC-248
17.	Tracer Studies with Inhaled Eight-day Iodine By M. Dailey, I. Wender, and R. Abrams	MDDC-251
18.	Tracer Studies with Inhaled 1.0 Year Ruthenium By M. Dailey, I. Wender, and R. Abrams	MDDC-420
19.	Acute Toxicity of Inhaled 275-day Ce ¹⁴⁴ By H. C. Seibert and R. Abrams	MDDC-329
20.	Studies on the Inhalation of Fissionable Materials and Fission Products and Their Subsequent Fate in Rats and Man By K. G. Scott, D. Axelrod, J. Crowley, H. C. Lanz, and J. G. Hamilton	MDDC-1276
21.	Metabolism and Distribution of Inhaled Plutonium in Rats By R. Abrams, H. C. Seibert, A. M. Potts, L. L. Forker, D. M. Greenberg, S. Postel, and W. Lohr	MDDC-677
22.	Acute Toxicity of Intubated Plutonium Deposited in the Lungs By R. Abrams, H. C. Seibert, L. L. Forker, D. M. Greenberg, H. Lisco, L. O. Jacobson, and Eric L. Simmons	CH-3875
23.	Metabolism of Plutonium in Rats* By K. Scott, H. Fisher, Dorothy Axelrod, J. Crowley, A. J. Barber, and J. G. Hamilton	MDDC-1018
24.	A Comparison of the Metabolism of Plutonium (Pu ²³⁸) in Man and the Rat By J. Crowley, H. C. Lanz, K. G. Scott, and J. G. Hamilton	CH-3589
25.	The Toxicity and Metabolism of Plutonium in Laboratory Animals I. Introduction By R. H. Snyder and R. D. Finkle II. Methods By R. H. Snyder and W. E. Kisieleski III. The Metabolism of Injected Plutonium By R. H. Snyder, W. E. Kisieleski, B. Lawrence, and R. D. Finkle IV. The Survival and Growth of Plutonium-Injected Animals By R. H. Snyder, W. E. Kisieleski, and R. D. Finkle V. The Effect of Ingested Plutonium By R. H. Snyder, B. Lawrence, and R. D. Finkle VI. The Hematological Effects of Parenterally Administered Plutonium By L. O. Jacobson and E. L. Simmons	MDDC-1140

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26.	The Effect of Plutonium on Tissue Metabolism of Rats By E. S. G. Barron, R. Abrams, R. D. Finkle, and R. P. Rhoades	MDDC-1653
27.	Combination of Plutonium with Plasma Proteins (Electrophoretic and Chemical Analysis) By J. A. Muntz and E. S. G. Barron	MDDC-1268
28.	The Metabolism of Thorium, ^(b) Protoactinium, ^(b) and Neptunium ^(b) in the Rat By H. Lanz, K. G. Scott, J. Growley, and J. G. Hamilton	MDDC-648
29.	The Production of Radioactive Xenon for Animal Exposures By R. Abrams, C. E. Beilman, and L. D. Norris	MDDC-1325
30.	The Maintenance of Animals Containing Radioactive Materials By P. Britton, P. Lear, C. L. Prosser, and E. Tyree	MDDC-1243
31.	Apparatus for Injection of Animals with Dangerous Amounts of Hard Beta and Gamma Emitters By D. S. Anthony and W. O. Norris	AECD-2007
32.	An Apparatus for Maintaining a Slow and Constant Rate of Injection By R. H. Snyder, B. Lawrence, and R. D. Finkle	MDDC-270
33.	The Administration of Radioactive Materials to Animals by Tracheal Intubation By H. C. Seibert	MDDC-268
34.	Accumulation and Distribution of Radioactive Strontium, Barium-Lanthanum, Fission Mixture and Sodium in Goldfish By C. L. Prosser, W. Pervinsek, J. Arnold, G. Svihla, and P. C. Tompkins	MDDC-496
35.	The Lethal Action of X Radiation, Stable Isotopes of Fission Elements, Sr ⁹⁰ and (Ba-La) ¹⁴⁰ , upon Goldfish ^(b) By C. L. Prosser, C. W. Hagen, Jr., and W. Grundhauser	MDDC-1480
36.	Plant Studies ^(b) (The Fixation and Absorption of Fission Products by Plants) By L. Jacobson and R. Overstreet	MDDC-571
37.	Absorption and Fixation of Fission Products and Plutonium by Plants By L. Jacobson and R. Overstreet	CH-3588
38.	The Metabolism of Short-lived Air-borne Fission Products By H. C. Lanz and J. D. Teresi	MDDC-954
39.	The Effect of Clay on the Intestinal Absorption of Strontium By H. J. Curtis	MDDC-419
40.	The Transmission of Radio-strontium and Plutonium from Mother to Offspring in Laboratory Animals ^(b) By M. P. Finkel	MDDC-750

Paper No.	Title ^(a) and Authors	Report No.
41.	Studies of the Metabolism and Toxic Action of Injected Radium I. Metabolism, Lethal Action and Clinical Changes By W. P. Norris and H. B. Evans	AECD-1965
	II. Hematological Effects of Parenterally Administered Radium. A Comparison of Plutonium and Radium Effects By L. O. Jacobson and E. L. Simmons	AECD-2372
42.	The Excretion, Retention, Distribution, and Clinical Effects of Strontium-89 in the Dog I. Report of Experimental Work By M. N. Swift and C. L. Prosser	MDDC-1388
	II. Statistical Analysis of Excretion and Retention for Individual Dogs By G. Sacher	AECD-2108
43.	Comparative Action of Injected Sr ⁸⁹ on Splenectomized and Non-splenectomized Mice By L. O. Jacobson and E. L. Simmons	CH-3886
44.	Acute Radiotoxicity of Injected Na ²⁴ for Mice and Rats I. Metabolism and General Toxicity By R. D. Finkle and R. H. Snyder	AECD-2011
	II. The Effect of the Na ²⁴ on the Leucocytes of the Peripheral Blood of Mice By L. O. Jacobson, and E. L. Simmons	AECD-2036
45.	Effects of Insoluble Ingested Y ⁹¹ I. Introduction: Methods By D. S. Anthony	
	II. Metabolism By D. S. Anthony and W. Grundhauser	
	III. Acute Lethal Action By D. S. Anthony	
	IV. Measurement of Dosage By D. S. Anthony, W. Grundhauser, and G. Svihla	
	V. Chronic Lethal Action By A. M. Brues and W. Grundhauser	
	VI. Effects on Weight By D. S. Anthony and W. Grundhauser	
	VII. Pathological Effects By H. Lisco and G. Sacher	
	VIII. Hematological Effects By L. O. Jacobson and E. L. Simmons	AECD-2037
46.	Clinical Physiology of Dogs Injected with Plutonium By Elizabeth E. Painter, E. R. Russell, C. L. Prosser, Marguerite N. Swift, W. E. Kisieleski, and G. Sacher	CH-3858
47.	Effects of Sr ⁸⁹ and X Radiation on Goats By Marguerite N. Swift, C. L. Prosser, and E. S. Mika (Contributions by Leon O. Jacobson, Herman Lisco, George Sacher, Roberta Edwards, La Forne Little, Homer Hipple, and Oscar Klioze)	AECU-108

Paper No.	Title ^(a) and Authors	Report No.
48.	Radioautographic Methods By G. Svihla	
49.	The Effect of Folic Acid on the Response of the Peripheral Blood and Blood-forming Tissue of the Rat to Parenterally Administered Sr ⁸⁹ By L. O. Jacobson, S. P. Stearner, E. L. Simmons, and M. H. Black	ANL-4126
50.	Plutonium in Puncture Wounds and Lacerations. A Preliminary Study By R. D. Finkle, J. D. Teresi, R. H. Snyder, and J. J. Nickson	

(a) The titles use the nomenclature of the time and have not been changed; this includes the designation of isotopes.

(b) Published also in the open literature.

(c) Part of AECD-2483

The reader must be impressed by the extent to which the papers listed indicate both breadth and depth of coverage of what was at the time an essentially new field. Large areas of research encountered in the post-World-War-II studies described in this book can be seen foreshadowed or actually begun in the work of the MED. While quality and polish may be somewhat deficient in some papers, this performance and others like it belie the accusation sometimes heard that the MED biomedical studies were largely "hack work." We learned an enormous amount in a short time. It is remarkable that only the small amount described above (and a few other isolated parcels) escaped preparation for and provision to posterity.

The broad outlines of the NNEs are as follows:

- Division I — Electromagnetic Separation Project
- Division II — Gaseous Diffusion Project
- Division III — Special Separations Project
- Division IV — Plutonium Project
- Division V — Los Alamos Project
- Division VI — University of Rochester Project
- Division VII — Materials Procurement Project
- Division VIII — Manhattan Project

Biomedical research appears primarily in volumes of Division IV and VI. The health volumes of Division IV are:

- Vol. 20 — Industrial Medicine (survey and collected papers)
- Vol. 22B, C — Effects of X and Gamma Rays
- Vol. 22D — Effects of Slow and Fast Neutrons
- Vol. 22E — Effects of External Beta Radiation
- Vol. 22F, G, H — Not published
- Vol. 22I — Histopathology of Irradiation from External and Internal Sources
- Vol. 23 — Toxicology of Uranium

The work reported in these volumes was accomplished at the Metallurgical Laboratory, University of Chicago; Clinton Laboratories, Oak Ridge; Crocker Laboratory, University of California, Berkeley; Hanford Engineer Works, Richland, Washington; and National Cancer Institute, Bethesda, Maryland. The editor for these health volumes was Raymond E. Zirkle, as remarked earlier. The volumes from Division VI (Rochester) were all in the health field. Those pertinent to internal emitter research were:

Vol. 1 — Pharmacology and Toxicology of Uranium Compounds
published in two major parts, 1949 and 1953, each
requiring two volumes in terms of binding, but not
numbering.

Vol. 3 — Biological Studies with Polonium, Radium, and Plutonium

There were also volumes concerning the external radiation studies done at Rochester.

Appendix D

Abbreviations and Acronyms

ABCC	Atomic Bomb Casualty Commission
ABM	Antiballistic missile
ACGIH	American Council of Governmental Industrial Hygienists
ACRH	Argonne Cancer Research Hospital
ACS	American Chemical Society
AD	Aerodynamic diameter
AEA	Atomic Energy Authority, U.K.
AEC	Atomic Energy Commission
AECD	Atomic Energy Commission Declassified (Report)
AERE	Atomic Energy Research Establishment, U.K.
AFRRI	Armed Forces Radiobiology Research Institute
ALARA	As low as reasonably achievable
AMAD	Activity median aerodynamic diameter
ANL	Argonne National Laboratory
ANP	Aircraft nuclear propulsion
ANS	American Nuclear Society
ANSI	American National Standards Institute
AVF	Asimuthally varying field
AWRE	Atomic Weapons Research Establishment, U.K.
BAL	British anti-lewisite
BaP	Benzo[a]pyrene
BCL	Battelle-Columbus; Battelle Memorial Institute's facility in Columbus, Ohio

BEAR	Committees and their reports on Biological Effects of Atomic Radiation, under U.S. National Academy of Sciences–National Research Council (1960s)
BEIR	Several committees of the National Academy of Sciences–National Research Council on Biological Effects of Ionizing Radiation and their reports. Usually followed by a Roman numeral. (1970s and 1980s)
BFWT	Body free-water tritium
BMI	Battelle Memorial Institute
BNL	Brookhaven National Laboratory
BNW	Battelle–Northwest; Battelle, Pacific Northwest Laboratories, Richland, Washington
BRH	Bureau of Radiological Health (for many years under the U.S. Public Health Service, later the U.S. Food and Drug Administration)
BWR	Boiling water reactor
CAL	California State Water Pollution Control Board
CARL	Comparative Animal Research Laboratory (later name for UT–AEC Farm)
CBF	Controlled background facility
CEA	Commissariat à l’Energie Atomique, France
CEC	Commission of the European Communities
CERT	Controlled environmental radioiodine release tests, Idaho Falls
CF	Concentration factor
CFR	Code of Federal Regulations
CH-	Chicago report (from MED days) followed by number
CMA	California Medical Association
CMD	Count median diameter
CNEN	Comitato Nazionale per l’Energia Nucleare, Italy
CR	Cumulative rad
CSU	Colorado State University
CUEX	Cumulative exposure index
CUMEX	Cumulative hazard index
CWLM	Cumulative working level month
DAAG	Dose Assessment Advisory Group
DASA	Defense Atomic Support Agency
DBER	Division of Biological and Environmental Research, DOE, ERDA
DBM	Division of Biology and Medicine, AEC
DF	Discrimination factor

DHEW	Department of Health, Education and Welfare
DHHS	Department of Health and Human Services
DNA	Defense Nuclear Agency; deoxyribonucleic acid
DoD	Department of Defense
DOE	Department of Energy
DOH	Division of Occupational Health, AEC
DTPA	Diethylenetriaminepentaacetic acid—a chelating agent
ECF	Extracellular fluid
EDDHA	Ethylenediamine di O-hydroxyphenylacetic acid
EDTA	Ethylenediaminetetraacetic acid—a chelating agent (followed by related agents, DTPA, DETA, and DFOA and their zinc or calcium salts, see chapter 19)
EF	Equilibrium factor
EG&G	Edgerton, Gormenhausen, and Grier
EIS	Environmental impact statement
EML	Environmental Measurements Laboratory (later name for the Health and Safety Laboratory in New York)
EPA	Environmental Protection Agency
ERDA	Energy Research and Development Administration
EULAP	European Late Effects Project Group
FAO	Food and Agricultural Organization
FAP	Fused aluminosilicate particles—used at ITRI as a carrier in aerosols
FASEB	Federation of American Societies for Experimental Biology
FDA	Food and Drug Administration
FIDLER	Field instrument for detection of low-energy radiation, a portable radiation survey instrument
FP	Fission products
FPFRT	Fission product field release test
FR	<i>Federal Register</i> , USA
FRC	Federal Radiation Council, USA. Also joint reports of the Federal Radiation Council–National Academy of Sciences
GPO	Government Printing Office
HASL	Health and Safety Laboratory of AEC in New York
HEEDTA	Hydroxyethylenediaminetriacetic acid
HEHF	Hanford Environmental Health Foundation
HPS	Health Physics Society
HTGR	High temperature gas-cooled reactor

HW	Hanford Works
IAEA	International Atomic Energy Agency, Vienna
ICRP	International Commission on Radiological Protection
ICRU	International Commission on Radiation Units and Measurements
INEL	Idaho National Engineering Laboratory
IRPA	International Radiation Protection Association
ITRI	Inhalation Toxicology Research Institute (Lovelace)
IUMRRG	Interagency Uranium Mining Radiation Review Group
JCAE	Joint Committee on Atomic Energy of the U.S. Congress
LASL (LANL)	Los Alamos Scientific Laboratory (now Los Alamos National Laboratory)
LBL	Lawrence Berkeley Laboratory
LD	Lethal dose
LET	Linear energy transfer
LLL (LLNL)	Lawrence Livermore Laboratory; Lawrence Livermore National Laboratory
LMFBR	Liquid metal fast breeder reactor
LOCA	Loss of coolant accident
MDDC	Manhattan District declassified report (from World-War-II days)
MED	Manhattan Engineer District (sometimes Manhattan Engineering District). The code name for the atomic bomb project during World War II.
Met Lab	The Metallurgical Laboratory, part of the MED
MGH	Massachusetts General Hospital
MIRD	Medical Internal Radiation Dose (a committee of the Society for Nuclear Medicine)
MIT	Massachusetts Institute of Technology
MMD	Mass median diameter
MPC	Maximum permissible concentration
MPCA	Minnesota Pollution Control Agency
MPI	Microcurie present initially
MRC	Medical Research Council, U.K.
M.U.	Mache unit
Mwe	Megawatts of electrical energy
NACOR	National Advisory Committee on Radiation
NAEG	Nevada Applied Ecology Group

NAS	National Academy of Sciences
NAS-NRC	National Academy of Sciences-National Research Council
NBS	National Bureau of Standards
NCI	National Cancer Institute
NCRP	National Council on Radiation Protection and Measurements, USA
NEA	Nuclear Energy Agency
NEPA	National Environmental Policy Act
NERP	National Environmental Research Park
NERVA	Nuclear engine for rocket vehicle application
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NNES	National Nuclear Energy Series. The series of volumes published by McGraw-Hill Book Company containing significant results of the MED research in all fields.
NOAA	National Oceanic and Atmospheric Administration
NRC	National Research Council; Nuclear Regulatory Commission
NRDC	Natural Resources Defense Council
NRDL	Naval Radiological Defense Laboratory, San Francisco
NRPB	National Radiological Protection Board, U.K.
NTS	Nevada Test Site
NVO	Nevada Operations Office, DOE
NYO	New York Operations Office, DOE
NYU	New York University
OEC	Organization for Economic Cooperation and Development
OHER	Office of Health and Environmental Research, DOE
ONR	Office of Naval Research
OR	Observed ratio
ORAU	Oak Ridge Associated Universities
ORINS	Oak Ridge Institute for Nuclear Studies
ORNL	Oak Ridge National Laboratory
ORO	Oak Ridge Operations Office, DOE
OSRD	Office of Scientific Research and Development
PAG	Protective action guide
PHA	Pulse height analyzer
PHS	Public Health Service

PNL	Pacific Northwest Laboratory, operated for DOE by Battelle Memorial Institute at Richland, Washington. Sometimes also "BNW" for Battelle-Northwest.
POR-WT	Project Officer's report—weapons tests
PPR	Plutonium Project record; Plutonium Project report
PRE	Pure radium equivalent
PUREX	Plutonium and uranium recovery through extraction
PWR	Pressurized water reactor
Ra A, - B, etc.	Old terminology for members of the radium decay series. Similar designations were used for other series.
RBE	Relative biological effectiveness
REECO	Reynolds Electrical and Engineering Company
RES	Reticuloendothelial system
RNA	Ribonucleic acid
ROVER	A nuclear rocket propulsion project.
RPG	Radiation protection guide
RTG	Radioisotope thermoelectric generator
SAG	Suggested action guide
SMR	Standardized mortality ratios
SNAP	Systems for nuclear auxiliary power
SREL	Savannah River Ecology Laboratory
SRL	Savannah River Laboratory
SRP	Savannah River Plant
SWRHL	Southwest Radiological Health Laboratory
SWRL	See SWRHL
TBLN	Tracheobronchial lymph nodes
TCT	Tissue-combined tritium
TEC	Tennessee Eastman Corporation
TFWT	Tissue free-water tritium
TG-57	Test Group-57 of Operation Plumbbob, NTS
TGLD	Task Group on Lung Dynamics (ICRP), sometimes TGLM for Task Group on Lung Model
TGLM	Task Group on Lung Model (ICRP), sometimes TGLD for Task Group on Lung Dynamics
TID	Technical Information document
TLD	Thermoluminescent dosimeter
TMP	Test Manager's Advisory Panel, NTS

TTR	Tonopah Test Range
TU	Transuranium
TVA	Tennessee Valley Authority
UC	University of California (branch usually follows)
UCLA	University of California, Los Angeles
UCRL	University of California Radiation Laboratory
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation
UR	University of Rochester
USAEC	See AEC
USAF	U.S. Air Force
USDA	U.S. Department of Agriculture
USDHEW	See DHEW
USDHHS	See DHHS
USDoD	See DoD
USDOE	See DOE
USEPA	See EPA
USERDA	See ERDA
USNRC	See NRC
USPHS	See PHS
USTR	U.S. Transuranium Registry
USUR	U.S. Uranium Registry
UT	University of Tennessee
UT-AEC	University of Tennessee-Atomic Energy Commission Farm, Oak Ridge
UW	University of Washington
WASH	Report from Washington Headquarters of AEC or subsequent agency
WHO	World Health Organization
WL	Working level
WLM	Working level month
WLY	Working level year

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